VOLUME 114

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AMERICAN JOURNAL OF OPHTHALMOLOGY

31

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• ORIGINAL ARTICLES

Anterior Proliferative Vitreoretinopathy
Lopez, Grossniklaus, Aaberg, Sternberg, Capone, Lambert

Levobunolol and Ocular Pulsatile Flow
Bosem, Lusky, Weinreb

Macular Phototoxicity
Michels, Lewis, Abrams, Han, Mieler, Neitz

Pattern Discrimination Perimetry
Nutaitis, Stewart, Kelly, Hunt, Severns

Pattern Discrimination Perimetry Fluctuation
Stewart, Kelly, Hunt

Vagal Responses to Suture Adjustment
Eustis, Eiswirth, Smith

Duane's Retraction Syndrome
von Noorden

Stereopsis and Congenital Monocular Cataract Extraction
Gregg, Parks

Ocular Forceps Injury
McDonald, Burgess

Myo-neuro-gastrointestinal Encephalopathy Syndrome
Threlkeld, Miller, Golnik, Griffin, Kuncl, Johns, Lehar, Hurko

Corneal Endothelial F-Actin
Kim, Geroski, Holley, Urken, Edelhauser

Ciprofloxacin-resistant Bacterial Keratitis
Snyder, Katz

Paraformaldehyde-induced Keratitis
Pallikaris, Tsilimbaris, Papatzanaki, Goles, Siganos

Optisol Corneal Storage Medium
Lindstrom, Kaufman, Skelnik, Laing, Lass, Musch, Trousdale, Reinhart, Burris, Sugar, Davis, Hirokawa, Smith, Gordon

• PERSPECTIVES

Ophthalmic Drug Development
Novack

• LETTERS TO THE JOURNAL

Detachment of Descemet's membrane
Macsai

Acquired intermittent jerk nystagmus
Miller, Younger, Friendly

Acetazolamide hypersensitivity
Peralta, Abelairas, Fernández-Guardiola

Lateral tarsorrhaphy
Bouchard

Fungal keratitis after radial keratotomy
Maskin, Alfonso

***Sporothrix schenckii* scleritis**
Brunette, Stulting

Nocardial scleritis
Brooks, Mills, Coster

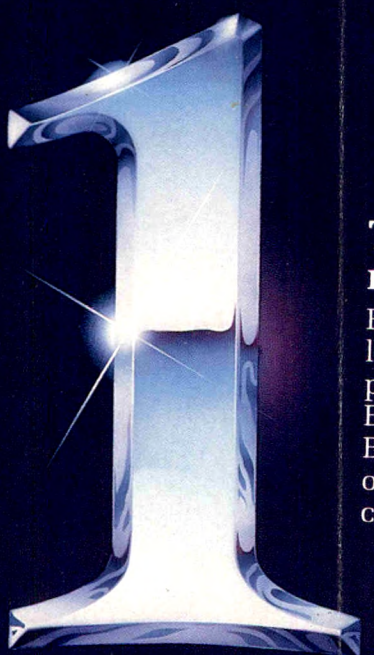
Preseptal cellulitis caused by *Nocardia brasiliensis*
Hunter, Krinsky, Fleener

Brucellosis and uveitis
Walker, Sharma, Rao

Herpesvirus 6 in retinitis
Reux, Fillet, Agut, Katlama, Hauw, LeHoang

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AJO® AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 September 1992 Series 3, Vol. 114, No. 3

TABLE OF CONTENTS

ORIGINAL ARTICLES

Pathogenetic mechanisms in anterior proliferative vitreoretinopathy
Pedro F. Lopez, Hans E. Grossniklaus, Thomas M. Aaberg, Paul Sternberg, Jr., Antonio Capone, Jr., and H. Michael Lambert 257

Short-term effects of levobunolol on ocular pulsatile flow
Marc E. Bosem, Moshe Lusky, and Robert N. Weinreb 280

Macular phototoxicity caused by fiberoptic endoillumination during pars plana vitrectomy
Mark Michels, Hilel Lewis, Gary W. Abrams, Dennis P. Han, William F. Mieler, and Jay Neitz 287

Pattern discrimination perimetry in patients with glaucoma and ocular hypertension
Matthew J. Nutaitis, William C. Stewart, Dolores M. Kelly, Hurshell H. Hunt, and Matthew L. Severns . 297

Long-term and short-term fluctuation in pattern discrimination perimetry
William C. Stewart, Dolores M. Kelly, and Hurshell H. Hunt 302

Vagal responses to adjustable sutures in strabismus correction
H. Sprague Eustis, Clement C. Eiswirth, and David R. Smith 307

Recession of both horizontal recti muscles in Duane's retraction syndrome with elevation and depression of the adducted eye
Gunter K. von Noorden 311

Stereopsis after congenital monocular cataract extraction
Fred M. Gregg and Marshall M. Parks 314

Contralateral occipital depression related to obstetric forceps injury to the eye
Marguerite B. McDonald and Stuart K. Burgess 318

Ophthalmic involvement in myo-neuro-gastrointestinal encephalopathy syndrome
Anisa B. Threlkeld, Neil R. Miller, Karl C. Golnik, John W. Griffin, Ralph W. Kuncl, Donald R. Johns, Mohamed Lehar, and Orest Hurko 322

Corneal endothelial cytoskeletal changes in F-actin with aging, diabetes, and after cytochalasin exposure
Eung K. Kim, Dayle H. Geroski, Glenn P. Holley, Steven I. Urken, and Henry F. Edelhauser 329

Ciprofloxacin-resistant bacterial keratitis
Michael E. Snyder and Harold R. Katz 336

Paraformaldehyde-induced keratitis after photorefractive keratectomy
Ioannis G. Pallikaris, Miltiades K. Tsilimbaris, Maria E. Papatzanaki, Konstantinos G. Goles, and Dimitrios S. Siganos 339

Optisol [illegible]storage medium
Richard L[illegible]ustrom, Herbert E. Kaufman, Debra L. Skelnik, Ronald A. Laing, Jonathan H. Lass, David C. Musch, Melvin D. Trousdale, William J. Reinhart, Terry E. Burris, Alan Sugar, Richard M. Davis, Kiminori Hirokawa, Tessie Smith, and Judy F. Gordon 345

PERSPECTIVES

The development of new drugs for ophthalmology
Gary D. Novack 357

LETTERS TO THE JOURNAL

Total detachment of Descemet's membrane after small-incision cataract extraction. *Marian S. Macsai,* **365. Treatment of acquired intermittent horizontal jerk nystagmus with baclofen.** *Bruce A. Miller, Deirdre A. Younger, and David S. Friendly,* **366. Anaphylactic shock and death after oral intake of acetazolamide.** *Jesús Peralta, José Abelairas, and José Fernández-Guardiola,* **367. Lateral tarsorrhaphy for a noncompliant patient with floppy eyelid syndrome.** *Charles S. Bouchard,* **367. Fungal keratitis after radial keratotomy.** *Steven L. Maskin and Eduardo Alfonso,* **369. *Sporothrix schenckii* scleritis.** *Isabelle Brunette and R. Doyle Stulting,* **370. Nocardial scleritis.** *James G. Brooks, Jr., Richard A. D. Mills, and Douglas J. Coster,* **371. Preseptal cellulitis caused by *Nocardia brasiliensis*.** *Lee R. Hunter, Andrew H. Krinsky, and Carola H. Fleener,* **373. Brucellosis and uveitis.** *Jonathan Walker, Om P. Sharma, and Narsing A. Rao,* **374. In situ detection of human herpesvirus 6 in retinitis associated with acquired immunodeficiency syndrome.** *Isabelle Reux, Anne-Marie Fillet, Henri Agut, Christine Katlama, Jean-Jacques Hauw, and Phuc LeHoang,* **375.**

CORRESPONDENCE

Prophylactic use of apraclonidine for intraocular pressure increase after Nd:YAG capsulotomies. *Andrew Romanowski,* **377. Reply.** *David E. Silverstone, Stephen F. Brint, Kenneth W. Olander, Robert B. Taylor, George R. McCarty, Joseph M. deFaller, and Linda L. Burk,* **378. Argon laser treatment of trichiasis.** *M. Douglas Gossman, Rudy Yung, A. Jan Berlin, Joseph R. Brightwell, and John W. Williams,* **379. Reply.** *George B. Bartley and Jonathan C. Lowry,* **380. Sculpting of hydroxyapatite implants—Correction.** *Mont J. Cartwright,* **380.**

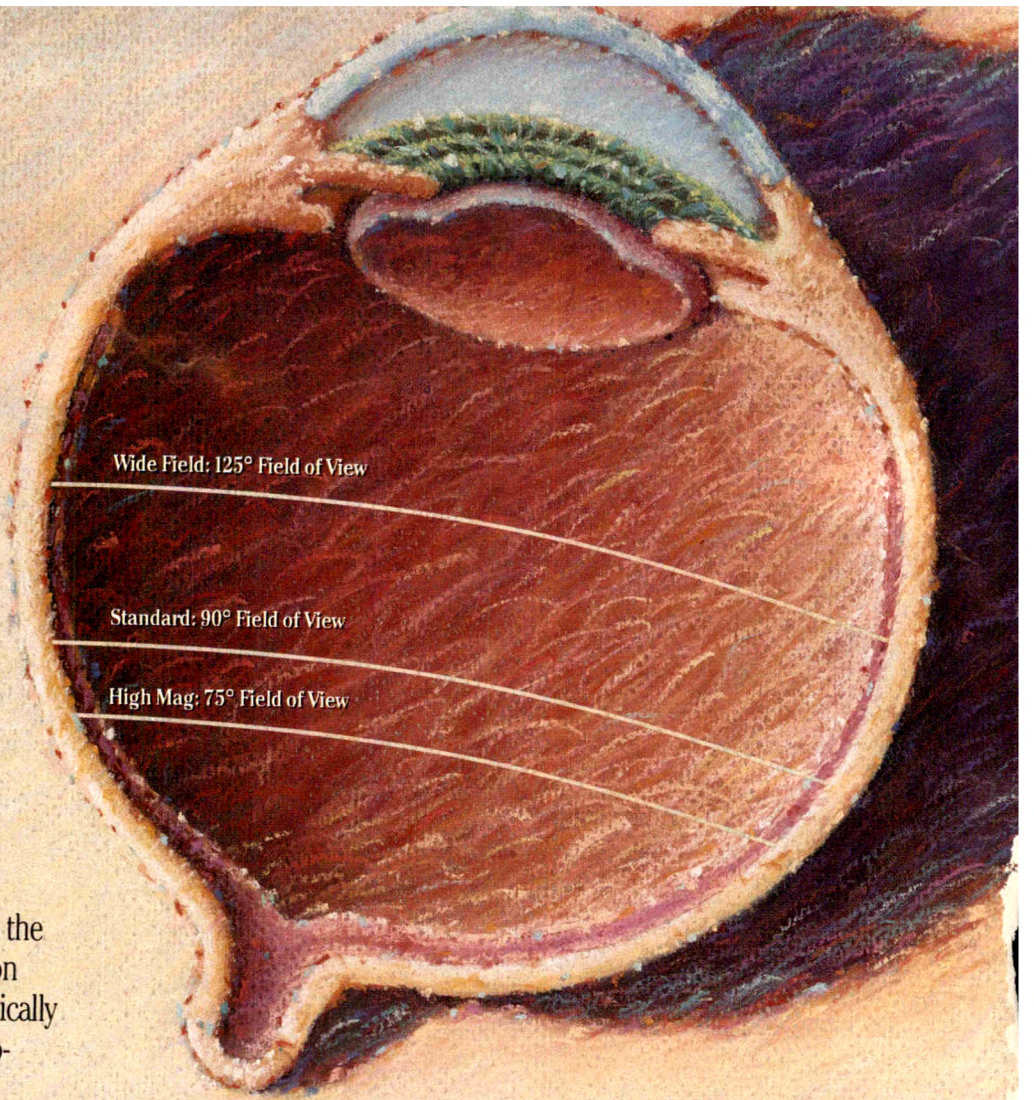
BOOK REVIEWS

Atlas of Orbital Surgery (Charles R. Leone, Jr., Arthur S. Grove, Jr., William C. Lloyd III, and Ted H. Wojno). *Reviewed by Jack Rootman,* **381. Clinical**

(Table of Contents continued on Advertising Page 8)

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AJO® AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 September 1992 Series 3, Vol. 114, No. 3

TABLE OF CONTENTS *(continued from Advertising page 6)*

Decisions in Neuro-Ophthalmology, ed. 2 (Ronald M. Burde, Peter J. Savino, and Jonathan D. Trobe). *Reviewed by Steven A. Newman,* **381. Fluorescein Angiography. Technique, Interpretation, and Application (Max Nanjiani).** *Reviewed by Steven Cohen,* **382. The Eye in General Practice, ed. 9 (C. R. S. Jackson and R. D. Finlay).** *Reviewed by Joshua Gutman,* **383. Spanish-English, English-Spanish Medical Dictionary (Onyria Herrera McElroy and Lola L. Grabb), 384.**

ABSTRACTS 385

NEWS ITEMS 393

CLASSIFIEDS . . . . . Begins on Advertising 51

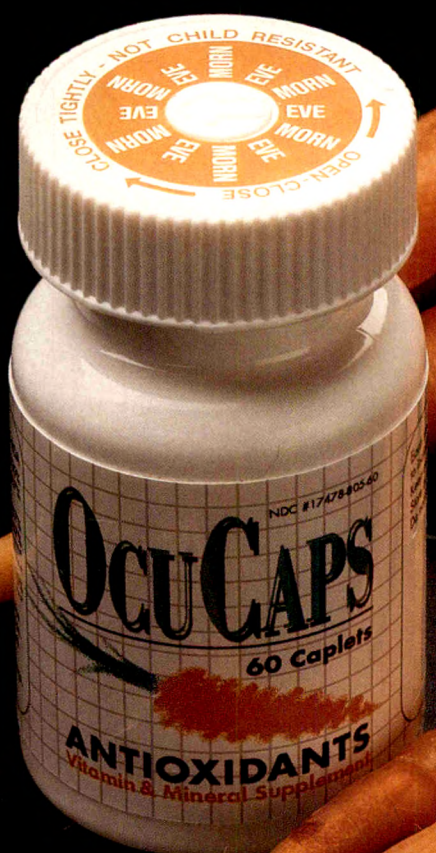
COPYRIGHT TRANSFER . . . . . Advertising 40

INSTRUCTIONS TO AUTHORS . . . . . Advertising 35

PRODUCTS AND SERVICES . . . . . Begins on Advertising 44

ADVERTISING INDEX . . . . . Advertising 54

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AJO® AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 October 1992 Series 3, Vol. 114, No. 4

TABLE OF CONTENTS

ORIGINAL ARTICLES

Glove perforations in ophthalmic surgery
Paul Prendiville, Peter J. McDonnell, and Paul P. Lee 397

Intraocular lens power calculations for multifocal intraocular lenses
Jack T. Holladay and Kenneth J. Hoffer 405

Results of late surgery for presumed congenital cataracts
Kenneth W. Wright, Laurie E. Christensen, and Barbara A. Noguchi 409

The Tokyo Metropolitan Home Vision Screening Program for amblyopia in 3-year-old children
Koji Yazawa, Junnosuke Suga, Shigeru Wakita, Masami Sumitomo, and Yasuo Uemura 416

Ocular hydrofluoric acid burns
Roy S. Rubinfeld, David I. Silbert, Juan J. Arentsen, and Peter R. Laibson 420

Stray light in radial keratotomy and the influence of pupil size and straylight angle
Henk G. N. Veraart, Thomas J. T. P. van den Berg, Jan K. IJspeert, and Oscar Lopes Cardozo 425

Photorefractive keratectomy for severe postkeratoplasty astigmatism
Mauro Campos, Lars Hertzog, Jenny Garbus, Martha Lee, and Peter J. McDonnell 429

Fungal keratitis from nylon line lawn trimmers
Thomas E. Clinch, Matthew J. Robinson, Bruce A. Barron, Michael S. Insler, Keith Liang, and Herbert E. Kaufman 437

Topical fibronectin in the treatment of keratoconjunctivitis sicca
J. Daniel Nelson, Judy F. Gordon, and the Chiron Keratoconjunctivitis Sicca Study Group 441

Progression of nonproliferative diabetic retinopathy and visual outcome after extracapsular cataract extraction and intraocular lens implantation
Glenn J. Jaffe, Thomas C. Burton, Evelyn Kuhn, Ardra Prescott, and Arthur Hartz 448

Efficacy of fluid-air exchange for postvitrectomy diabetic vitreous hemorrhage
Daniel F. Martin and Brooks W. McCuen II 457

Immunohistochemical and histochemical properties of surgically excised subretinal neovascular membranes in age-related macular degeneration
Hans E. Grossniklaus, Jose A. Martinez, Vonita B. Brown, H. Michael Lambert, Paul Sternberg, Jr., Antonio Capone, Jr., Thomas M. Aaberg, and Pedro F. Lopez 464

Aqueous dynamics in exfoliation syndrome
N. Ziai Gharagozloo, Robert H. Baker, and Richard F. Brubaker 473

Intraocular pressure decrease in household contacts of patients with Hansen's disease and endemic control subjects
N. Hussein, T. Chiang, Q. Ehsan, and R. Hussain . . . 479

Asymmetric pigmentary glaucoma resulting from cataract formation
Robert Ritch, Teekhasaenee Chaiwat, and Thomas S. Harbin, Jr. 484

The edrophonium-Hess screen test in the diagnosis of ocular myasthenia gravis
Gustavo E. Coll and Joseph L. Demer 489

Behr's syndrome and 3-methylglutaconic aciduria
R. N. Sheffer, J. Zlotogora, O. N. Elpeleg, J. Raz, and D. Ben-Ezra 494

PERSPECTIVES

Neuro-ophthalmic associations and complications of diabetes mellitus
Ronald M. Burde 498

LETTERS TO THE JOURNAL

Use of the Potential Acuity Meter in suspected functional visual loss. *Leah Levi and Robert M. Feldman,* **502. Corneoscleral, ciliary body, and vitreoretinal toxicity after excessive instillation of mitomycin C.** *Satish Gupta and Surendra Basti,* **503. Pure ocular blast injury.** *Itzchak Beiran and Benjamin Miller,* **504. Mild frosted branch periphlebitis.** *David J. Browning,* **505. Retinal neovascularization and cystoid macular edema in punctata albescens retinopathy.** *Shimon Rumelt, Eliezer Kraus, and Uri Rehany,* **507. Subretinal diathermy probe.** *Gholam A. Peyman and Nalin J. Mehta,* **508. Idiopathic alternating anisocoria.** *Michael C. Brodsky, Gregory B. Sharp, Katherine J. Fritz, and James J. Corbett,* **509. Inflammatory orbital tumor as an ocular sign of a battered child.** *William Waterhouse, Robert W. Enzenauer, and Vernon C. Parmley,* **510. Malignant myoepithelioma after radiation for retinoblastoma.** *Stephen J. Saxe, Hans E. Grossniklaus, and Ayten O. Someren,* **512. Periosteal flap for lower eyelid reconstruction.** *Charles R. Leone, Jr.,* **513.**

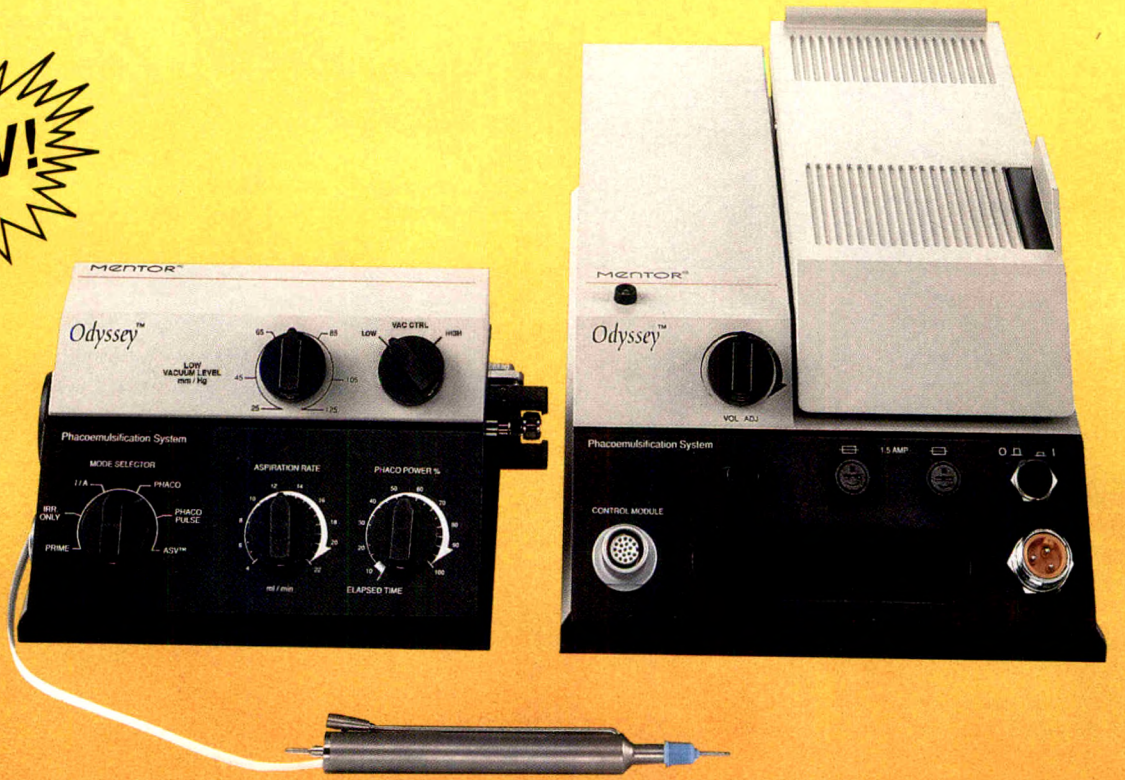
CORRESPONDENCE

Frosted branch angiitis associated with cytomegalovirus retinitis. *Stephan A. Geier, Joachim Nasemann, Volker Klauss, Ursula Kronawitter, and Frank D. Goebel,* **514. Reply.** *Richard F. Spaide, Albert T. Vitale, Ilona R. Toth, and Jorge M. Oliver,* **515. Ultrasound biomicroscopy of anterior segment structures in normal and glaucomatous eyes.** *Albert M. Bezzina,* **516. Reply.** *Charles J. Pavlin, Kasia Harasiewicz, and F. Stuart Foster,* **517.**

(Table of Contents continued on Advertising Page 8)

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ISSN 0002-9394 October 1992 Series 3, Vol. 114, No. 4

TABLE OF CONTENTS *(continued from Advertising page 6)*

BOOK REVIEWS

Grayson's Diseases of the Cornea, ed. 3 (Robert C. Arffa). *Reviewed by Ronald D. Plotnik,* **518. The Surgical Rehabilitation of Vision (Edited by Lee T. Nordan, W. Andrew Maxwell, and James A. Davison).** *Reviewed by Erich Groos,* **518. Neuro-Ophthalmology. A Practical Text (Nancy M. Newman).** *Reviewed by Robert T. Spector,* **519. The Changing Visual System. Maturation and Aging in the Central Nervous System (Edited by P. Bagnoli and W. Hodos), 520. Corneal Alterations With Contact Lens Wear (A. J. P. Rouwen), 520. Diabetic Retinopathy. A Slide-Script Program (American Academy of Ophthalmology), 520. Medical Malpractice. Handling Ophthalmology Cases (Sander Marc Rabin), 520.**

ABSTRACTS 521

NEWS ITEMS 529

CLASSIFIEDS . . . . . Begins on Advertising 54

COPYRIGHT TRANSFER . . . . . Advertising 34

INSTRUCTIONS TO AUTHORS . . . . . Advertising 41

PRODUCTS AND SERVICES . . . . . Begins on Advertising 50

ADVERTISING INDEX . . . . . Advertising 57

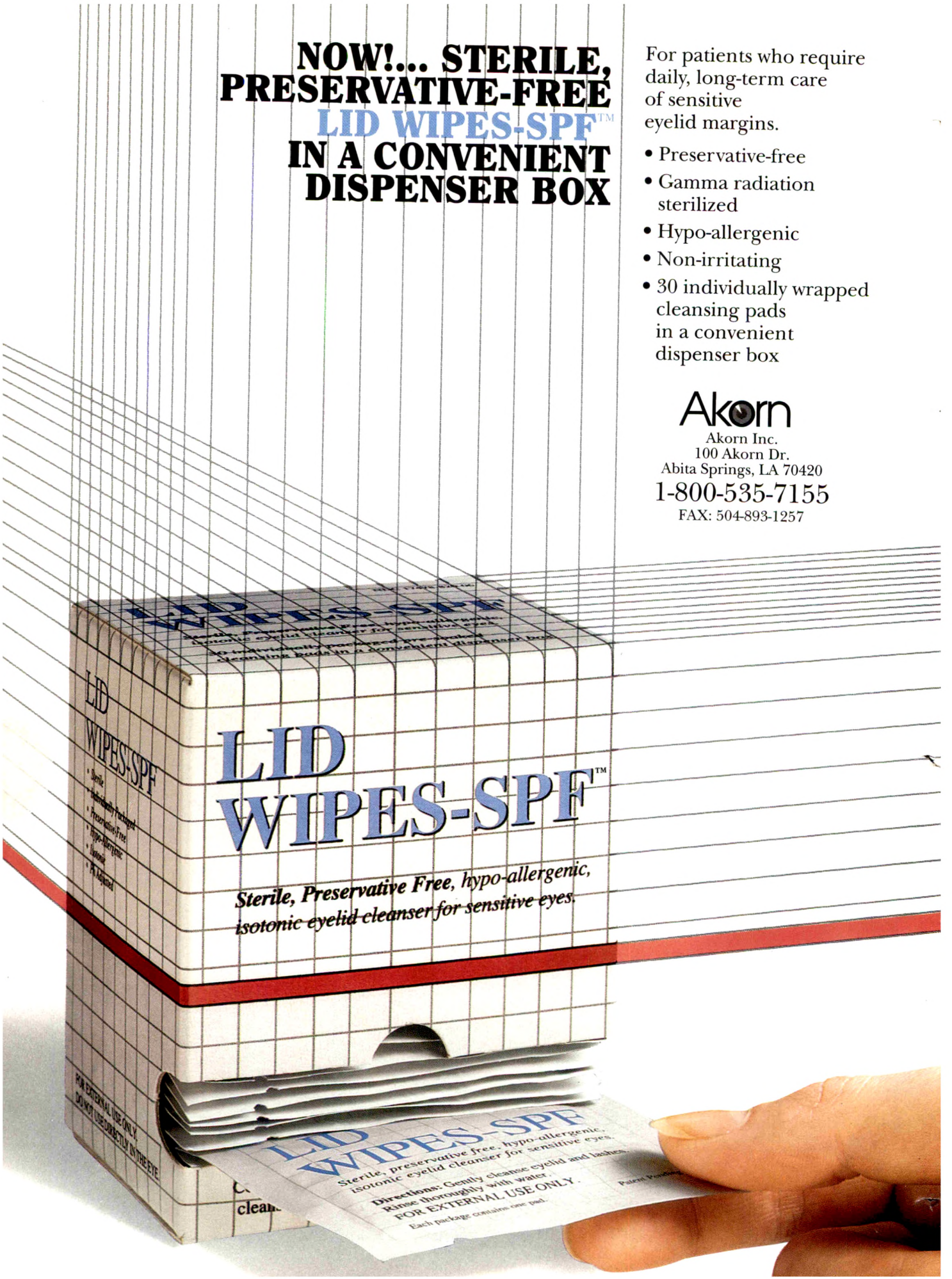
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AJO® AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 November 1992 Series 3, Vol. 114, No. 5

TABLE OF CONTENTS

ORIGINAL ARTICLES

Community care of corneal ulcers
Peter J. McDonnell, Janis Nobe, W. James Gauderman, Paul Lee, Amy Aiello, and Melvin Trousdale 531

Lattice degeneration of the retina and the pigment dispersion syndrome
Peter Weseley, Jeffrey Liebmann, Joseph B. Walsh, and Robert Ritch 539

Hypotonous maculopathy after trabeculectomy with subconjunctival 5-fluorouracil
Robert L. Stamper, Matthew G. McMenemy, and Marc F. Lieberman 544

Changes in optic disk characteristics and the number of nerve fibers in experimental glaucoma
Rohit Varma, Harry A. Quigley, and Mary Ellen Pease 554

The influence of exposure duration in transscleral Nd:YAG laser cyclophotocoagulation
Bruce E. Prum, Jr., Steven R. Shields, Ruthanne B. Simmons, David A. Echelman, and M. Bruce Shields 560

Acquired oculomotor, trochlear, and abducent cranial nerve palsies in pediatric patients
Sylvia R. Kodsi and Brian R. Younge 568

Development of object vision in infants with permanent cortical visual impairment
Teresa C. Chen, Margot H. Weinberg, Robert A. Catalano, John W. Simon, and William A. Wagle 575

Ocular findings in Cockayne syndrome
Elias I. Traboulsi, Inge De Becker, and Irene H. Maumenee 579

Orbital cellulitis caused by *Eikenella corrodens*
Ramzi Hemady, Amy Zimmerman, Brett W. Katzen, and James W. Karesh 584

Diode laser photocoagulation for prethreshold, posterior retinopathy of prematurity
Thomas N. Fleming, Paul E. Runge, and Steven T. Charles 589

Posterior segment changes in membranoproliferative glomerulonephritis
David D. Kim, William F. Mieler, and Mitchell D. Wolf 593

Posterior capsulotomy as a complication of indirect laser photocoagulation
Vinod Lakhanpal, Deeba Husain, and Stanley S. Schocket 600

Polymerase chain reaction for the detection of the varicella-zoster genome in ocular samples from patients with acute retinal necrosis
Mauro Nishi, Rodolfo Hanashiro, Shigeo Mori, Kanjiro Masuda, Manabu Mochizuki, and Ryo Hondo 603

Retained lens fragments after phacoemulsification manifesting as marked intraocular inflammation with hypopyon
W. David Irvine, Harry W. Flynn, Jr., Timothy G. Murray, and Patrick E. Rubsamen 610

Vogt-Koyanagi-Harada syndrome in patients with Cherokee Indian ancestry
Jose A. Martinez, Pedro F. Lopez, Paul Sternberg, Jr., Thomas M. Aaberg, H. Michael Lambert, Antonio Capone, Jr., Barry A. Mandell, and Nancy J. Newman 615

Conjunctival involvement in paraneoplastic pemphigus
Stephanie J. Meyers, Gary A. Varley, David M. Meisler, Charles Camisa, and Arden H. Wander 621

Optic neuropathy in Hodgkin's disease
R. Michael Siatkowski, Byron L. Lam, Norman J. Schatz, Joel S. Glaser, Sandra F. Byrne, and J. Randall Hughes 625

EDITORIAL

Divergent approaches to the management of corneal ulcers
Jay S. Pepose and Kirk R. Wilhelmus 630

LETTERS TO THE JOURNAL

Ultrastructure of human immunodeficiency virus in corneal epithelial scraping. *Bruce L. Johnson and Andrew E. Holzman,* **633. Propofol and surgical contamination in strabismus surgery.** *Dorothy V. Bautista and Ronald V. Keech,* **635. Vertical fusion amplitude in normal adults.** *Kumudini Sharma and Aziz S. Abdul-Rahim,* **636. *Moraxella* infection of a scleral buckle.** *David Callanan and Patrick E. Rubsamen,* **637. Severe anaphylactic reaction after indocyanine green fluorescence angiography.** *Sebastian Wolf, Oliver Arend, Karin Schulte, and Martin Reim,* **638. Intraconjunctival cavitary inclusions of silicone oil complicating retinal detachment repair.** *Sean P. Donahue, Thomas R. Friberg, and Bruce L. Johnson,* **639. Conjunctival concretions.** *Vera O. Kowal, Anthony P. Adamis, and Daniel M. Albert,* **640. Development of a retinal artery macroaneurysm at the site of a previously detected retinal artery embolus.** *Robert A. Wiznia,* **642. Nonbacterial thrombotic endocarditis and cortical blindness.** *James A. Rush,* **643. Visual recovery after radiation therapy of orbital lymphoma.** *Darius M. Moshfeghi, Paul T. Finger, Ronald B. Cohen, Woomyung Choe, and Thom Smilari,* **645.**

CORRESPONDENCE

Successful therapy for trilateral retinoblastoma. *Gregg T. Lueder,* **646. Reply.** *Steven C. Nelson, Henry S. Friedman, W. Jerry Oakes, Edward C. Halperin, Robert Tien, Gregory N. Fuller, Beverly Hockenberger, Mark*

(Table of Contents continued on Advertising Page 8)

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AJO® AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 November 1992 Series 3, Vol. 114, No. 5

TABLE OF CONTENTS *(continued from Advertising page 6)*

W. Scroggs, Mark Moncino, Joanne Kurtzberg, and Edward G. Buckley, **647. Successful therapy for trilateral retinoblastoma.** *David H. Abramson,* **647. Reply.** *Steven C. Nelson, Henry S. Friedman, W. Jerry Oakes, Edward C. Halperin, Robert Tien, Gregory N. Fuller, Beverly Hockenberger, Mark W. Scroggs, Mark Moncino, Joanne Kurtzberg, and Edward G. Buckley,* **648. Multifunction endolaser probe.** *Stanley Chang,* **648. Reply.** *Gholam A. Peyman and Kwang J. Lee,* **648. The obligation of ophthalmic organizations to report their actions.** *George L. Spaeth,* **649.**

BOOK REVIEWS

Ocular Emergencies (Robert A. Catalano). *Reviewed by David Chaffin,* **650. Optics and Refraction. A User-Friendly Guide (David Miller).** *Reviewed by David L. Guyton,* **650. Atlas of Ophthalmic Surgery, volume II. Oculoplastic, Lacrimal, and Orbital Surgery (Jonathan J. Dutton).** *Reviewed by Richard Bensinger,* **651. The Lazy Eye. A Simulation Environment for Neuro-Ophthalmology. Computer software (Howard S. Bregman, Phong T. Ly, and Steven Galetta).** *Reviewed by R. D. Cunningham,* **651. The Fragile Species (Lewis Thomas).** *Reviewed by H. Stanley Thompson,* **652. Decision Making in Ophthalmology (Edited by W. A. J. van Heuven and Johan T. Zwaan), 653. Enzymology of The Tears (Andras Berta), 653. Fundamentals of Ophthalmic Practice. Ethics and Economics. Office and Risk Management (Stephan A. Kamenotzky), 653. Management and Treatment of Benign Cutaneous Vascular Lesions (Edited by Oon Tian Tan), 653.**

ABSTRACTS 654

NEWS ITEMS 662

CLASSIFIEDS . . . . . Begins on Advertising 54

COPYRIGHT TRANSFER . . . . . Advertising 40

INSTRUCTIONS TO AUTHORS . . . . . Advertising 35

PRODUCTS AND SERVICES . . . . . Begins on Advertising 50

ADVERTISING INDEX . . . . . Advertising 57

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ISSN 0002-9394 December 1992 Series 3, Vol. 114, No. 6

TABLE OF CONTENTS

ORIGINAL ARTICLES

Racial differences in the prevalence of intraocular lens implants in the United States
Catherine M. Sharkness, Stanford Hamburger, Ronald G. Kaczmarek, Peggy M. Hamilton, Roselie A. Bright, and Roscoe M. Moore, Jr. 667

11-0 Mersilene as running suture for penetrating keratoplasty
Beatrice E. Frueh, Stuart I. Brown, and Sandy T. Feldman 675

Ocular involvement in an outbreak of herpes gladiatorum
Edward J. Holland, Robert L. Mahanti, Edward A. Belongia, Martin W. Mizener, Jesse L. Goodman, Charles W. Andres, and Michael T. Osterholm 680

The use of polymerase chain reaction for the detection of chlamydial keratoconjunctivitis
Audrey R. Talley, Francisco Garcia-Ferrer, Keith A. Laycock, Michael Loeffelholz, and Jay S. Pepose . . 685

Surgical management of myokymia of the superior oblique muscle
Luis C. de Sa, William V. Good, and Creig S. Hoyt . . 693

Intraocular fluid cultures after primary pars plana vitrectomy
Steven M. Cohen, Jeffrey D. Benner, Maurice B. Landers III, and Lawrence S. Morse 697

Criteria to detect minimal expressivity within families with autosomal dominant aniridia
Helen A. Mintz-Hittner, Robert E. Ferrell, Leslie A. Lyons, and Frank L. Kretzer 700

Causes of reduced visual acuity on long-term follow-up after cataract extraction in patients with uveitis and juvenile rheumatoid arthritis
Gregory M. Fox, Harry W. Flynn, Jr., Janet L. Davis, and William Culbertson 708

Prediction of visual recovery after scleral buckling of macula-off retinal detachments
Thomas R. Friberg and Andrew W. Eller 715

Prevalence and risk factors of diabetic retinopathy among noninsulin-dependent diabetic subjects
Muh-Shy Chen, Chie-Shung Kao, Chih-Jen Chang, Ta-Jen Wu, Chen-Chung Fu, Chien-Jen Chen, and Tong-Yuan Tai 723

Cytokines in the vitreous of patients with proliferative diabetic retinopathy
Ahmed M. Abu El Asrar, Davide Maimone, Peter H. Morse, Susan Gregory, and Anthony T. Reder 731

Results of intraoperative 5-fluorouracil supplementation on trabeculectomy for open-angle glaucoma
M. Fran Smith, Mark B. Sherwood, J. William Doyle, and Peng T. Khaw 737

Intravitreal foscarnet for cytomegalovirus retinitis in a patient with acquired immunodeficiency syndrome
Manuel Díaz-Llopis, Enrique Chipont, Santiago Sanchez, Enrique España, Amparo Navea, and Jose L. Menezo 742

Ultrastructural findings in an autopsy eye from a patient with Usher's syndrome type II
Eliot L. Berson and Michael Adamian 748

Visual field defects in patients with normal-tension glaucoma and patients with high-tension glaucoma
John H. Zeiter, Dong H. Shin, Mark S. Juzych, Tim S. Jarvi, Thomas C. Spoor, and Fred Zwas 758

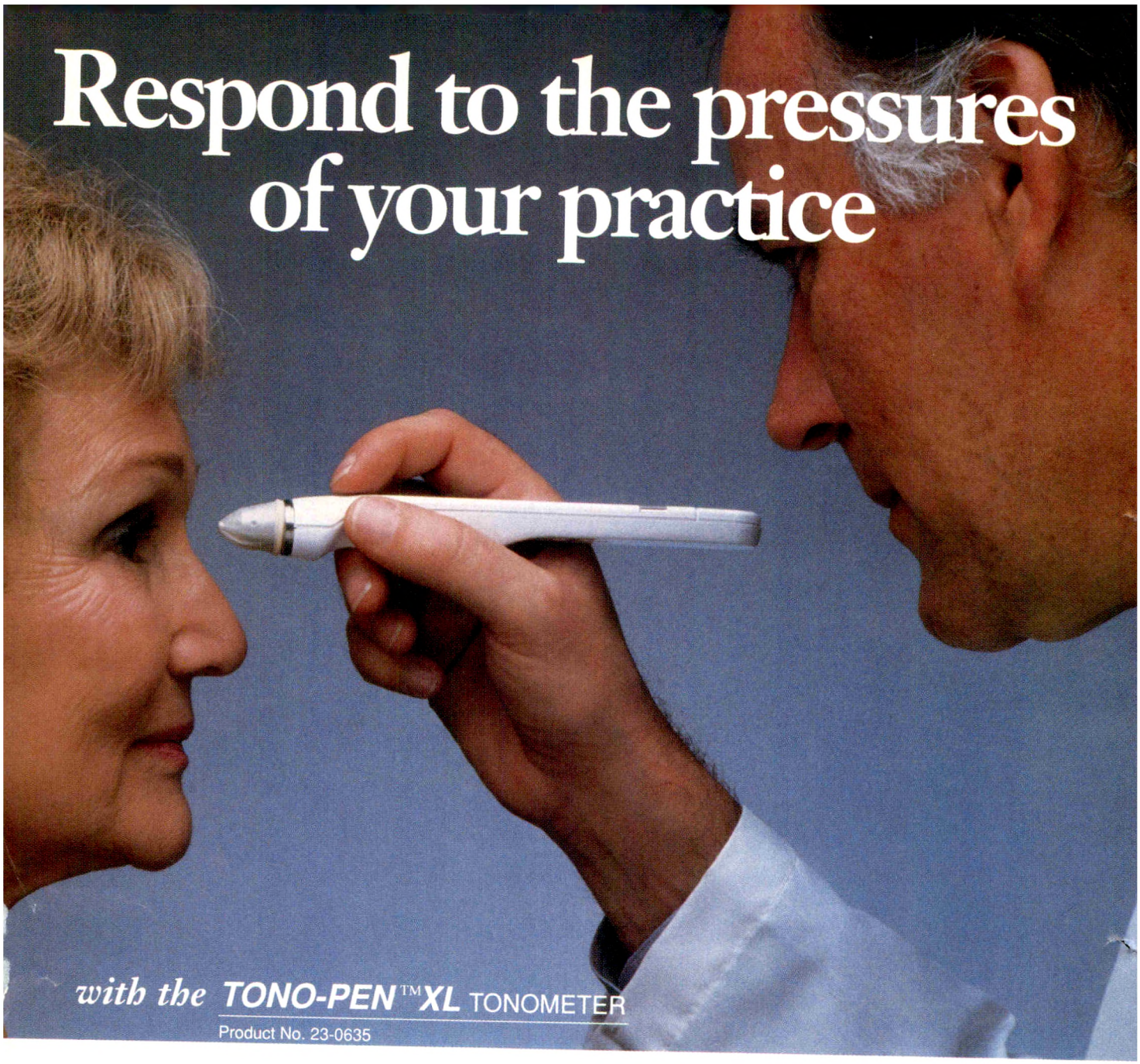
LETTERS TO THE JOURNAL

Low-tension glaucoma in identical twins. *Steven Ofner and John R. Samples,* **764. Impending macular hole associated with topical pilocarpine.** *William L. Benedict and Michel Shami,* **765. The association of iridoschisis and angle-recession glaucoma.** *John F. Salmon,* **766. Vitreous pulsations, relative hypotony, and retrobulbar cyst associated with a congenital optic pit.** *Thomas R. Friberg and Thomas G. McLellan,* **767. Spontaneous retinal reattachment in a patient with persistent hyperplastic primary vitreous and an optic nerve coloboma.** *Michel Shami, David McCartney, William Benedict, and Charles Barnes,* **769. Late-onset sterile endophthalmitis after Molteno tube implantation.** *Katrinka L. Heher, Jennifer I. Lim, Julia A. Haller, and Henry D. Jampel,* **771. *Xanthomonas maltophilia* endophthalmitis after implantation of sustained-release ganciclovir.** *Sanford Chen, Edward M. Stroh, Kenneth Wald, and Alex Jalkh,* **772. Bilateral panuveitis, sebopsoriasis, and secondary syphilis in a patient with acquired immunodeficiency syndrome.** *Sasikala Pillai and Francis DiPaolo,* **773. Bilateral radiant damage to the cornea and retina after exposure to a 700-V electric discharge.** *Kip Dolphin and Harvey Lincoff,* **775. Parabulbar anesthesia.** *Scott Greenbaum,* **776.**

CORRESPONDENCE

Causes and prognosis in 4,278 cases of paralysis of the oculomotor, trochlear, and abducens cranial nerves. *James A. Rush,* **777. Reply.** *B. W. Richards, F. R. Jones, and B. R. Younge,* **777. Apraclonidine and argon laser trabeculoplasty.** *Steven Ofner, John R. Samples, and E. Michael van Buskirk,* **778. Reply.** *P. C. Holmwood, R. D. Chase, T. Krupin, L. F. Rosenberg, J. M. Ruderman, B. A. Tallman, D. E. Brodstein, H. Chopra, and M. Goldenfeld,* **778. Molded acrylic mouthguard to control bleeding at the hard palate graft site after eyelid reconstruction.** *Norman Shorr and Yoash R. Enzer,* **779. Reply.** *J. A. Maurillo, Jr., B. Wasserman, S. Allee, and L. Robinson,* **780. Sudden retinal manifes-**

(Table of Contents continued on Advertising Page 8)



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AJO® AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 December 1992 Series 3, Vol. 114, No. 6

TABLE OF CONTENTS *(continued from Advertising page 6)*

tations of intranasal cocaine and methamphetamine abuse. *John H. Zeiter, Donna M. Corder, Mathew P. Madion, and John G. McHenry,* **780.**

BOOK REVIEWS

Ocular Pathology. A Color Atlas, ed. 2 (Myron Yanoff and Ben S. Fine). *Reviewed by Robert Folberg,* **782. Color Atlas of Ophthalmic Surgery. Oculoplastic Surgery (Edited by David T. Tse).** *Reviewed by Allen M. Putterman,* **782. Ocular Problems in Diabetes Mellitus (Edited by Stephen S. Feman).** *Reviewed by Mark J. Mannis,* **783. Current Practice in Ophthalmology (Edited by Andrew P. Schachat).** *Reviewed by Wing Chu,* **784. Management and Care of the Cataract Patient (Edited by Frank J. Weinstock).** *Reviewed by William Simcoe,* **785. Computerized Perimetry. A Simplified Guide, ed. 2 (Marc F. Lieberman and Michael V. Drake).** *Reviewed by Robb R. Schrader,* **785.**

ABSTRACTS 787

NEWS ITEMS 795

CLASSIFIEDS . . . . . Begins on Advertising 44

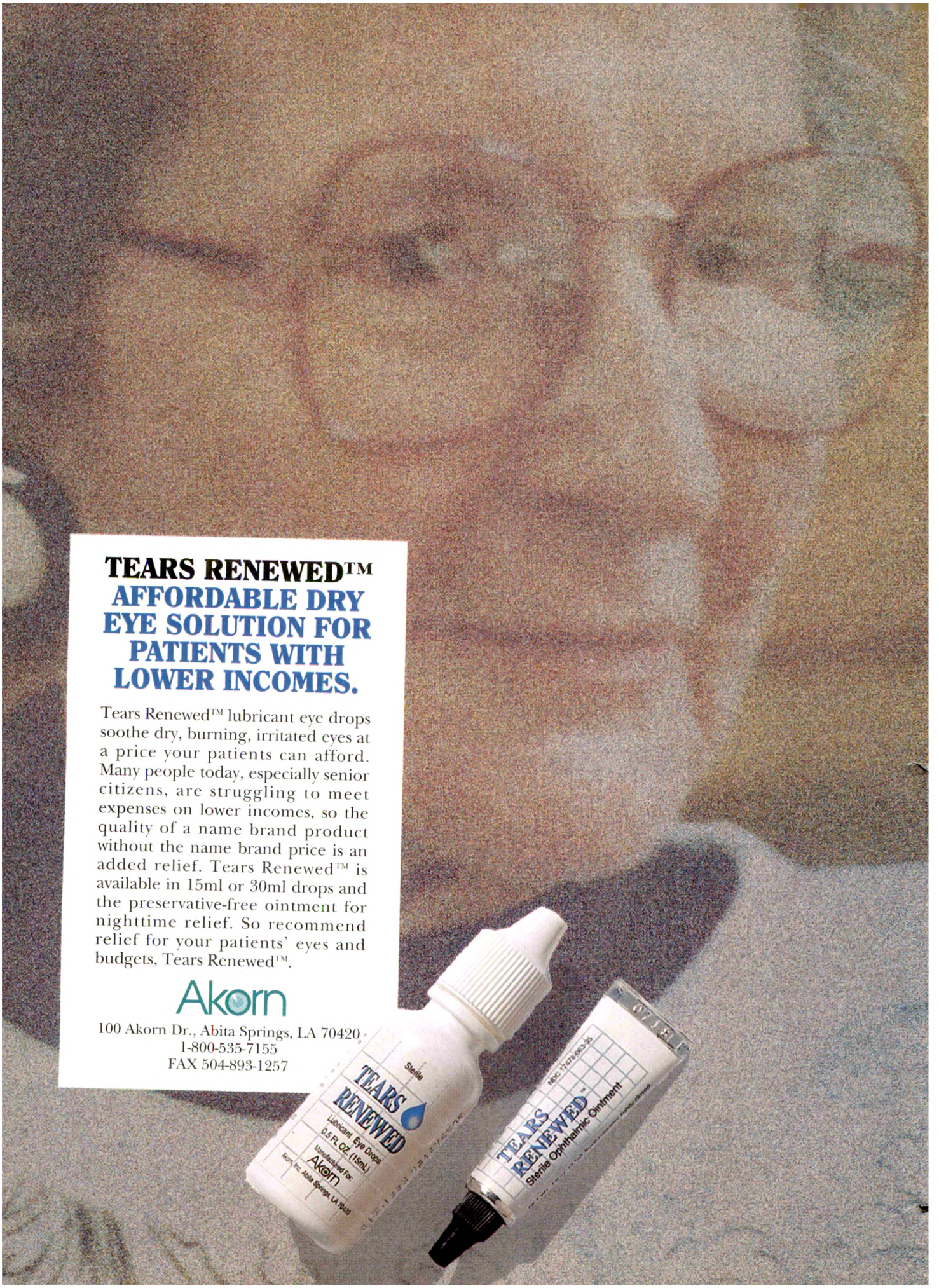
COPYRIGHT TRANSFER . . . . . Advertising 34

INSTRUCTIONS TO AUTHORS . . . . . Advertising 25

PRODUCTS AND SERVICES . . . . . Begins on Advertising 38

ADVERTISING INDEX . . . . . Advertising 47

INDEX i


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Pathogenetic Mechanisms in Anterior Proliferative Vitreoretinopathy

Pedro F. Lopez, M.D., Hans E. Grossniklaus, M.D., Thomas M. Aaberg, M.D., Paul Sternberg, Jr., M.D., Antonio Capone, Jr., and H. Michael Lambert, M.D.

A clinicopathologic study of ten consecutive patients (ten eyes) undergoing surgery for rhegmatogenous retinal detachment with anterior proliferative vitreoretinopathy and a subsequent histopathologic, immunohistochemical, and ultrastructural study of ten enucleated eyes with anterior proliferative vitreoretinopathy were performed in order to elucidate relevant pathogenetic mechanisms. Our findings suggest that the pathogenetic evolution of anterior proliferative vitreoretinopathy occurs in three consecutive stages: (1) traction on the ciliary body and peripheral retina induced by fibrocellular contraction of the vitreous base; (2) incorporation of tractionally denuded components of the ciliary body and peripheral retina into the fibrocellular membranes overlying the vitreous base; and (3) proliferation of the incorporated components and fibrovascular ingrowth from the uvea, the retina, or both, into the fibrocellular membranes. Tractional disruption of the epithelium of the ciliary body pars plicata and breakdown of the ciliary blood-aqueous barrier are the principal pathogenetic mechanisms of chronic intractable hypotony and the postvitrectomy fibrin syndrome in anterior proliferative vitreoretinopathy.

PROLIFERATIVE VITREORETINOPATHY is the most common cause of anatomic failure of primary surgery for rhegmatogenous retinal detachment and occurs in approximately 7% of cases.[1,2] Anterior proliferative vitreoretinopathy, defined as cellular proliferation with contraction occurring at or anterior to the posterior insertion of the vitreous base,[3] is the most common cause of failure to achieve retinal reattachment after both initial and repeat vitreoretinal surgery for proliferative vitreoretinopathy.[4,5] Using currently available vitreous base dissection techniques, retinal reattachment may be attained in up to 80% of these eyes.[4,5]

Anterior proliferative vitreoretinopathy consists of adherent vitreous and sheetlike membranes extending from the peripheral retina in the region of the posterior insertion of the vitreous base and attaching to the ciliary body, the posterior iris surface, the pupillary margin, or the cornea.[3,6] The clinical effects of this proliferation on the retina have been well described with respect to the variety of retinal folding configurations and their causative tractional forces. Anteroposterior contraction of the proliferative membranes drags the underlying peripheral retina anteriorly, producing a circumferential trough of variable width and depth between the circumferential retinal fold and the ciliary body.[3,6] Circumferential contraction produces fixed, pleated radial retinal folds extending from the circumferential retinal trough.[3,6] Perpendicular contraction results in an anterior retinal funnel of variable size.[6]

The effects of anterior proliferative vitreoretinopathy on intraocular structures anterior to the retina and the effects of current vitreous base dissection techniques[4-6] on these tissues are poorly understood. Some of the pathologic features of anterior proliferative vitreoretinopathy were described in one report[7]; however, that study included eyes that had prior trauma. Recurrent epiciliary proliferation is known to occur and may result in chronic hypotony in some eyes despite retinal reattachment.[8-12] The pathogenetic mechanism responsible for this phenomenon is unclear. Additionally, postvit-

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From the Department of Ophthalmology (Drs. Lopez, Grossniklaus, Aaberg, Sternberg, Capone, and Lambert); and the L. F. Montgomery Ophthalmic Pathology Laboratory (Dr. Grossniklaus), Emory University, Atlanta, Georgia. This study was supported in part by an unrestricted department grant from Research to Prevent Blindness, Inc., New York, New York, and departmental core grant EY06360. Dr. Lopez was a 1990–1991 Heed-Knapp Ophthalmic Fellow and a 1991–1992 Heed-Knapp Ophthalmic Fellow.

Reprint requests to Hans E. Grossniklaus, M.D., L. F. Montgomery Ophthalmic Pathology Laboratory, Rm. 1603, 1327 Clifton Rd. N.E., Atlanta, GA 30322.

rectomy fibrin syndrome (that is, excessive intraocular fibrin deposition) appears to be common in eyes with anterior proliferative vitreoretinopathy, particularly in those eyes in which anterior vitreous base dissection is performed.[18] The pathogenetic mechanism of this phenomenon is likewise unknown.

We undertook a clinicopathologic study of ten consecutive patients who underwent either initial or repeat vitreoretinal surgery for nontraumatic rhegmatogenous retinal detachment and anterior proliferative vitreoretinopathy. The purpose of the study was to determine the composition of surgically excised anterior proliferative vitreoretinopathy membranes and to evaluate the histopathologic effects of currently used vitreous base dissection techniques. We also performed a subsequent histopathologic study of ten enucleated eyes with longstanding, nontraumatic rhegmatogenous retinal detachment, hypotony, and anterior proliferative vitreoretinopathy to understand better the pathogenesis and surgical management of anterior proliferative vitreoretinopathy with hypotony.

Material and Methods

A clinicopathologic study was performed in ten patients with anterior proliferative vitreoretinopathy who underwent pars plana vitrectomy for rhegmatogenous retinal detachment between Aug. 1, 1990, and July 1, 1991. Eyes with proliferative vitreoretinopathy secondary to retinal vascular disease, inflammatory disease, trauma, or a history of previous intraocular silicone oil injection were excluded. Eyes with silicone oil injection were excluded because previous studies concerning the pathologic findings of eyes with proliferative vitreoretinopathy were performed before the widespread use of intraocular silicone oil. Best-corrected visual acuity, anterior and posterior segment examination findings, and ocular tension were recorded during the preoperative and postoperative examinations. Anterior and posterior proliferative vitreoretinopathy was defined and graded according to the classification proposed by Machemer and associates[14] with the modification that the division between anterior and posterior proliferative vitreoretinopathy was the posterior insertion of the vitreous base. The surgical techniques used in the dissection of the anterior and posterior proliferative vitreoretinopathy have been previously described.[3-6] Regional sampling of proliferative vitreoretinopathy membranes from different intraocular areas was done whenever possible. Proliferative vitreoretinopathy membranes obtained from different locations were classified as follows: anterior (anterior to the posterior insertion of the vitreous base), equatorial (from the region anterior to the vortex vein ampullae to the posterior insertion of the vitreous base), or posterior (from the region posterior to the vortex vein ampullae). Regional sampling of equatorial and posterior proliferative vitreoretinopathy was done in six of the ten eyes with anterior proliferative vitreoretinopathy. Since no significant ultrastructural differences existed between regional specimens from the equator or posterior pole, specimens from these two subgroups were collectively analyzed as posterior proliferative vitreoretinopathy. Each regional specimen was immediately fixed in separate 2.5% glutaraldehyde for electron microscopic processing. The specimens were post-fixed with 0.1mol/l cacodylate buffer and 1% osmium tetroxide after two hours. After standard dehydration, the specimens were embedded in epoxy resin. Semithin (1.0 μm) sections were cut and stained with uranyl acetate and lead citrate. Previously published criteria were used for ultrastructural identification of cells including ciliary epithelium, astrocytes, fibrocytes, lymphocytes, macrophages, myofibroblasts, retinal pigment epithelium, vascular endothelium, and extracellular material including collagen, fibrin, and internal limiting membrane.[15-17]

In order to put the ultrastructural findings of individual biopsy specimens into anatomic context, enucleated eyes were examined histopathologically to define the in situ relationship between the biopsy specimens of anterior proliferative vitreoretinopathy and the surrounding tissues. Ten enucleated eyes with longstanding total rhegmatogenous retinal detachment, chronic hypotony, and anterior proliferative vitreoretinopathy that had been accessioned between 1989 and 1990 in the L. F. Montgomery Ophthalmic Pathology Laboratory were examined as the comparison group. The eyes had all been fixed in 4% formalin and embedded in paraffin. Representative 7-μm thick slides from the center (pupil-optic nerve section) of each eye stained with hematoxylin and eosin were studied. Clinical histories and photographs were evaluated. All eyes with evidence of retinal vascular disease, inflammatory disease, trauma, silicone oil injection, or severe phthisis bulbi were excluded. Representative 7-μm sections were cut from each block and

placed on poly-l-lysine coated slides for immunohistochemical staining. Sections from each case were stained by using the standard avidin-biotin complex technique[18] with antibodies to the following antigens: glial fibrillary acid protein (1:400, Dako, Carpinteria, California), *Ulex europaeus* (1:200 and 1:500, Dako, Carpinteria, California), neuron specific enolase (1:400, Dako, Carpinteria, California), leukocyte common antigen (1:500, Dako, Carpinteria, California), and S-100 protein (1:400, Dako, Carpinteria, California). Appropriate positive and negative controls were performed. The blocks from each case were then deparaffinized, and tissue from the anterior proliferative vitreoretinopathy was placed in 2.5% glutaraldehyde and submitted for electron microscopic processing as described.

Results

Vitrectomy specimens—The mean age of the ten patients from whom the anterior proliferative vitreoretinopathy membrane biopsy specimens were taken was 47.6 years (range, 15 to 80 years). Six patients were males and four were females (Table 1). The predisposing conditions for retinal detachment included cataract extraction with vitreous loss in six eyes, lattice degeneration in two, congenital cataract extraction in one, and iatrogenic giant retinal tear in one. All the eyes had previous cataract extraction either through the corneoscleral limbus or pars plana before surgery for anterior proliferative vitreoretinopathy. Five eyes were pseudophakic and five were aphakic at the time of surgery for anterior proliferative vitreoretinopathy. Three of the pseudophakic eyes had anterior chamber intraocular lenses and two had posterior chamber intraocular lenses. One of the five aphakic eyes had an intracorneal lens. All eyes previously had encircling scleral buckles and limbal or pars plana vitrectomies. The average number of prior pars plana vitrectomies was one (range, zero to four). The one patient without a prior pars plana vitrectomy had a previous anterior vitrectomy during cataract extraction complicated by vitreous loss. The average interval between previous vitrectomy and anterior proliferative vitreoretinopathy dissection was 2.5 months (range, one to six months).

Complete retinal reattachment was achieved intraoperatively in all ten eyes. Seven of the ten eyes maintained retinal reattachment during a mean follow-up of 9.6 months (range, six to 12 months). Three eyes developed recurrent proliferative vitreoretinopathy and retinal detachment. Two of these eyes required further surgery. One patient declined further surgical intervention. All of the eyes with recurrent retinal detachment were from the group with postoperative ocular tensions greater than or equal to 10 mm Hg.

Preoperatively, all eyes had applanation ocular tensions of less than 10 mm Hg, with an average of 5 mm Hg (range, 1 to 9 mm Hg). Seven eyes had applanation ocular tensions of 5 mm Hg or less, which was the definition of hypotony in this study. The average ocular tension of the ten eyes increased postoperatively to 12 mm Hg (range, 1 to 27 mm Hg). Three of the seven eyes gained postoperative ocular ten-

TABLE 1
CLINICAL FEATURES OF TEN PATIENTS WITH VITRECTOMY FOR ANTERIOR PROLIFERATIVE VITREORETINOPATHY

CASE NO., AGE (YRS), GENDER	EYE	OCULAR TENSION (MM HG)		FOLLOW-UP (MOS)
		PREOPERATIVE	POSTOPERATIVE	
1, 56, M	R.E.	9	27	11
2, 77, M	R.E.	2	15	10
3, 76, M	L.E.	5	1	11
4, 50, M	L.E.	2	3	10
5, 56, F	R.E.	1	5	12
6, 66, F	L.E.	9	19	12
7, 15, M	L.E.	5	12	9
8, 80, F	R.E.	5	15	8
9, 50, M	L.E.	8	13	6
10, 73, F	L.E.	4	4	7

sions of 12 mm Hg or greater (range, 12 to 15 mm Hg). The remaining four eyes with preoperative hypotony had persistent postoperative hypotony. In these eyes ocular tension increased in two eyes, remained unchanged in one eye, and decreased in one eye postoperatively. Preoperative and postoperative gonioscopy failed to disclose the presence of cyclodialysis clefts in any of the ten eyes. Neither detachment of the ciliary body nor ciliochoroidal effusion was noted in any of the ten eyes studied clinically.

Preoperative clinical findings in the ten eyes with anterior proliferative vitreoretinopathy included forward displacement of the vitreous base with trough formation in eight, a dilated fixed pupil in eight, aqueous flare in eight, posterior iris retraction in seven, corneal stromal thickening and edema with Descemet's folds (striate keratopathy) in four, entropion uveae (posterior traction of the iris) in two, aqueous cells in two, rubeosis iridis in two, and Soemmering-ring lens remnants in two.

Two preoperative clinical signs were uniformly found in eyes with persistent postoperative hypotony: striate keratopathy and the presence of a circumferential ring of opaque, white, fibrous anterior proliferative vitreoretinopathy membranes that extended to and attached at or anterior to the pars plicata. All four eyes with corneal stromal edema and striate keratopathy had persistent postoperative hypotony despite retinal reattachment and the absence of an identifiable cyclodialysis cleft. In contrast, all six eyes without preoperative striate keratopathy achieved a postoperative ocular tension of 12 mm Hg or greater.

The circumferential extent of the proliferative vitreoretinopathy anterior to the posterior insertion of the vitreous base (anterior proliferative vitreoretinopathy) averaged 11.6 clock hours (range, 8 to 12 clock hours). The most anterior extent of the opaque, white, fibrous component of the anterior proliferative vitreoretinopathy, precisely defined only after surgical dissection, was the pars plana of the ciliary body in six eyes, the posterior iris surface in two eyes, and the cornea in two eyes. The presence of a circumferential ring of opaque, white, fibrous anterior proliferative vitreoretinopathy that extended to and attached at or anterior to the pars plicata was found in all four eyes with persistent postoperative hypotony, whereas all six eyes in which the most anterior extent of the opaque membranes was confined to the pars plana region achieved postoperative applanation ocular tensions of 12 mm Hg or greater. In contrast, eyes with diaphanous, forwardly displaced vitreous adherent to either the iris, the pars plicata, or both, commonly regained normal ocular tensions postoperatively. Diaphanous vitreous adherent to the pars plicata, the iris, or both, was often present as the forward extension of the opaque white fibrous component of the anterior proliferative vitreoretinopathy in the six eyes that regained normal ocular tension. In these eyes, the opaque white fibrous component of the anterior proliferative vitreoretinopathy was confined to the pars plana region.

Anteroposterior contraction of the anterior proliferative vitreoretinopathy was the predominant tractional force in all ten eyes. Circumferential contraction was a significant secondary tractional force in eight of the ten eyes. Perpendicular traction was insignificant in all

TABLE 2
ULTRASTRUCTURAL FEATURES OF SURGICALLY EXCISED PROLIFERATIVE VITREORETINOPATHY MEMBRANES FROM TEN PATIENTS* WITH ANTERIOR PROLIFERATIVE VITREORETINOPATHY

CELL TYPES	ANTERIOR PROLIFERATIVE VITREORETINOPATHY (N=10)	POSTERIOR PROLIFERATIVE VITREORETINOPATHY (N=6)
Ciliary body nonpigmented epithelium	7	0
Ciliary body pigmented epithelium	4	0
Fibrous astrocytes	3	1
Fibrocytes	2	4
Macrophages	3	4
Lymphocytes	0	1
Myofibroblasts	1	1
Retinal pigment epithelium	1	5
Endothelium-lined vascular channels	3	0
Fibrin	3	0
Internal limiting membrane	0	4
Lens remnants	2	0
Native collagen	6	3
New collagen	6	5
Retinal fragments	2	0
Iris fragments	1	0

*Six of the ten patients with anterior proliferative vitreoretinopathy had concurrent posterior proliferative vitreoretinopathy.

cases, in general because surgical removal of the anterior hyaloid had been performed during previous cataract extraction or vitrectomy.

Posterior proliferative vitreoretinopathy, behind the posterior insertion of the vitreous base, was also present in all ten eyes. The circumferential extent of posterior proliferative vitreoretinopathy was 12 clock hours in five eyes, six to eight clock hours in three eyes, and two to four clock hours in two eyes. There was no clinical evidence of fibrovascular ingrowth from the sclerotomy sites in any eye.

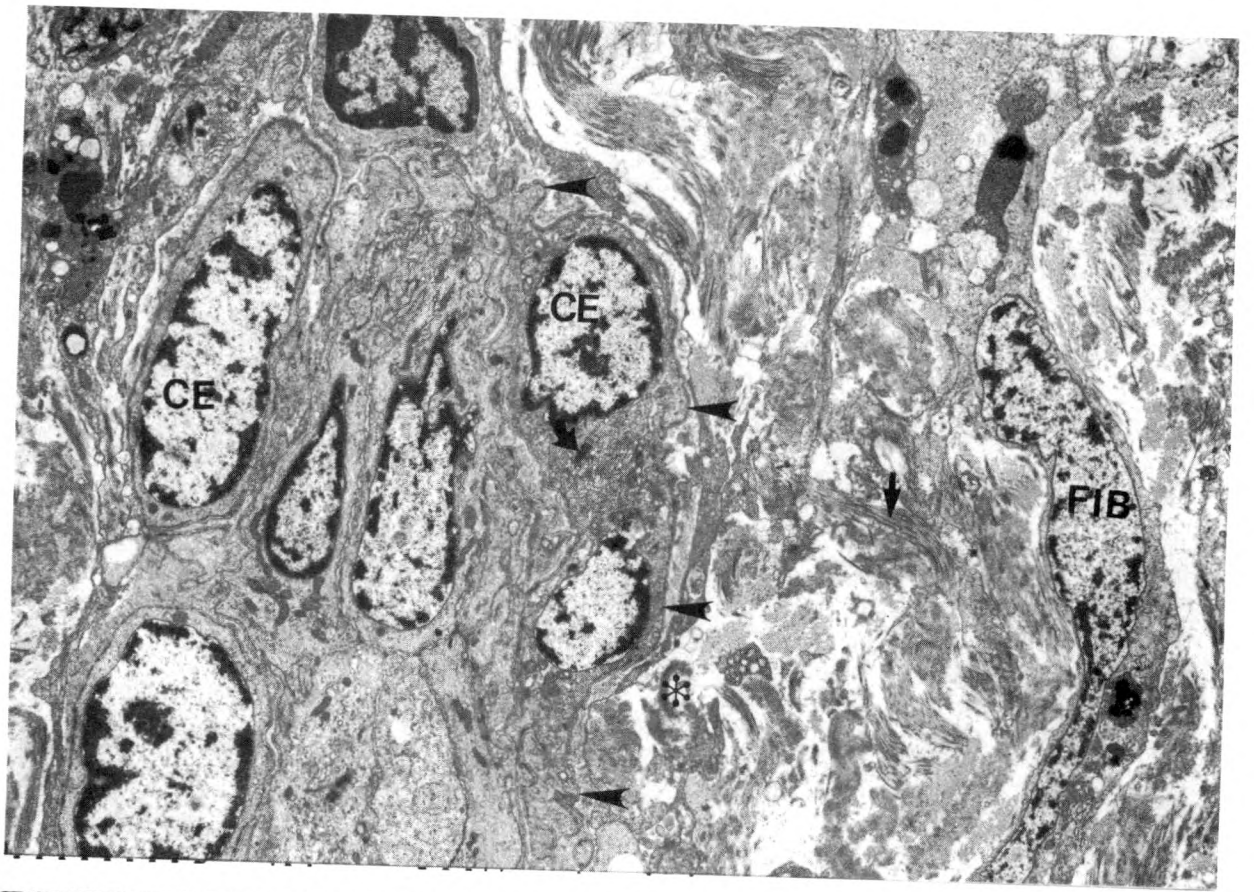
Although surgically excised anterior proliferative vitreoretinopathy membranes had ciliary epithelium ultrastructurally as the predominant cell type, ciliary body nonpigmented epithelium was present in seven of the specimens, and pigmented epithelium was present in four (Table 2). Ciliary epithelium was not found in any specimens of coexisting posterior proliferative vitreoretinopathy. In general, the ciliary epithelium in the anterior proliferative vitreoretinopathy membranes was present in sheets (Fig. 1), from which occasional ciliary epithelial cells budded or were pinched off and became incorporated into the adjacent fibrocellular stroma. Occasionally, isolated intact monolayer fragments of ciliary epithelium, devoid of accompanying fibrocellular tissue, were surgically excised (Fig. 2). All four eyes with chronic postoperative hypotony of 5 mm Hg or less had ciliary epithelium present within their anterior proliferative vitreoretinopathy membranes. The eyes that lacked ciliary epithelium in their membranes had postoperative ocular tensions of 10 mm Hg or greater. The finding of ciliary epithelium in vitrectomy specimens was not inevitably predictive of hypotony because four eyes with ciliary epithelium in their anterior proliferative vitreoretinopathy membranes had postoperative ocular tensions of 10 mm Hg or greater.

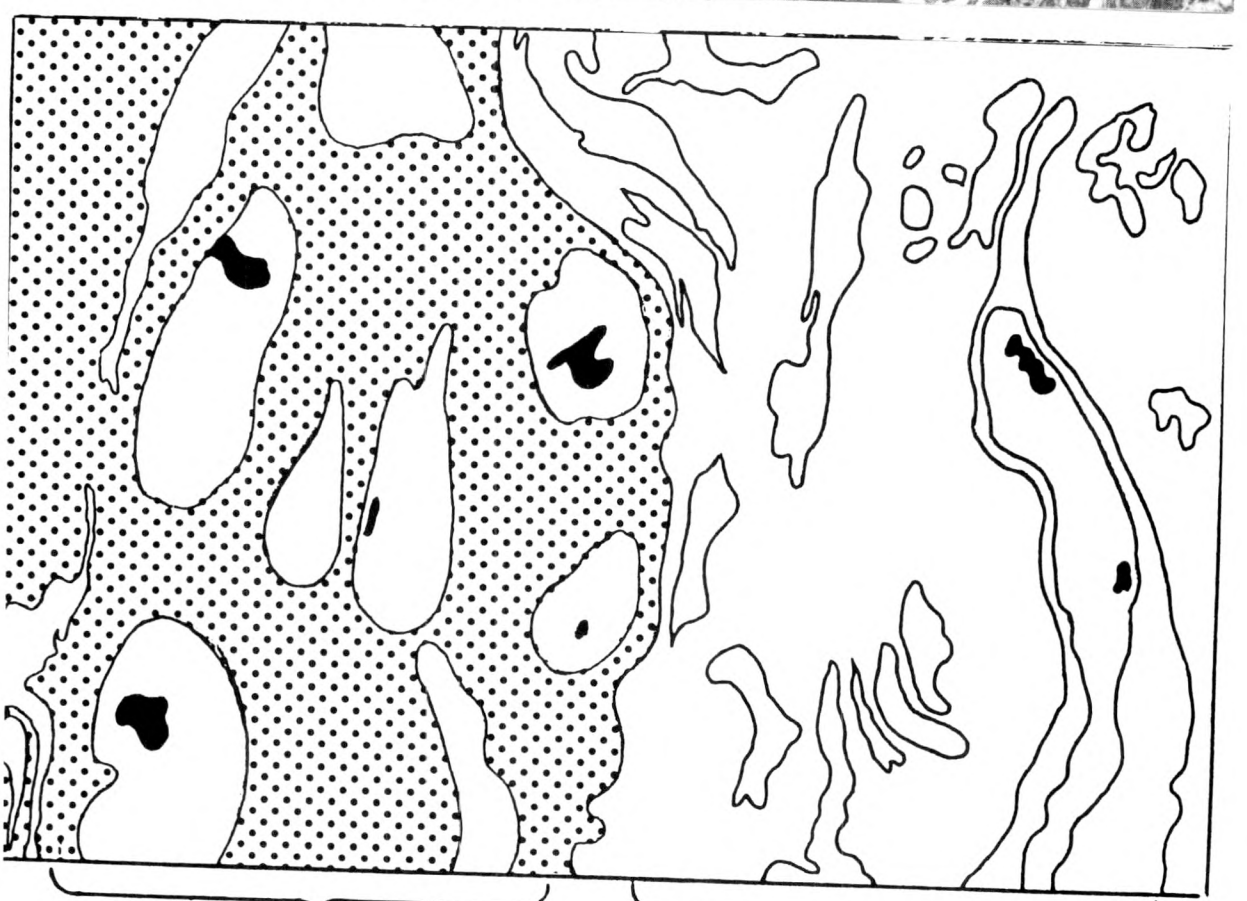
Other cell types present in the fibrocellular stroma of the surgically excised anterior proliferative vitreoretinopathy membranes were fibrous astrocytes in three (Fig. 3), macrophages in three, fibrocytes in two, myofibroblasts in one, and retinal pigment epithelium in one. These cell types were similar to those present in coexistent posterior proliferative vitreoretinopathy; however, the frequency of the cell types in the latter was different. The predominant cell types present in the coexistent posterior proliferative vitreoretinopathy were retinal pigment epithelium in five, fibrocytes in four, and macrophages in four. Fibrous astrocytes in one, lymphocytes in one, and myofibroblasts in one accounted for the remainder of the cellular components of the posterior proliferative vitreoretinopathy membranes.

The extracellular components of both the anterior and posterior proliferative vitreoretinopathy membranes were composed of original vitreous collagen, new collagen, or both. The extracellular component of ten anterior membranes was composed of original vitreous collagen in six, new collagen in six, or both in three. Degeneration of one anterior membrane prevented identification of the collagen type. Two patients who had both original vitreous and new collagen in their anterior membranes had chronic postoperative hypotony. The third patient with chronic postoperative hypotony had only original vitreous collagen in the anterior membrane. The extracellular component of the six posterior membranes included old collagen in two, new collagen in two, or both in two.

Other ultrastructural findings that were present in the surgically excised anterior proliferative vitreoretinopathy membranes but not in surgically excised posterior proliferative vitreoretinopathy membranes included endothelium-lined vascular channels in three eyes, fibrin in three, retinal fragments in two, lens remnants in two, and iris fragments in one. In all of the eyes with endothelium-lined vascular channels there was associated persistent postoperative hypotony. In one patient, the endothelium-lined vascular channels were associated with iris fragments. This patient had anterior proliferative vitreoretinopathy extending to the posterior iris surface. Retinal fragments unassociated with endothelium-lined vascular channels were found in the anterior proliferative vitreoretinopathy of one patient who required retinotomy, but postoperatively regained normal ocular tension.

In three eyes fibrin in the surgically excised anterior proliferative vitreoretinopathy was located either within the fibrous matrix of the membrane stroma (Fig. 4) or between the membrane stroma. Other incorporated ocular tissue included iris fragments found in one eye or multilaminar ciliary epithelium, found in two eyes. The presence of fibrin was associated with chronic postoperative hypotony in only one patient in whom opaque, dense, white, fibrous anterior proliferative vitreoretinopathy was attached to the posterior iris surface. The fibrin was interposed between an excised partial thickness iris fragment and the anterior proliferative vitreoretinopathy. The only ultrastruc-





SHEET OF CILIARY EPITHELIUM

VITREOUS BASE WITH FIBROCYTE

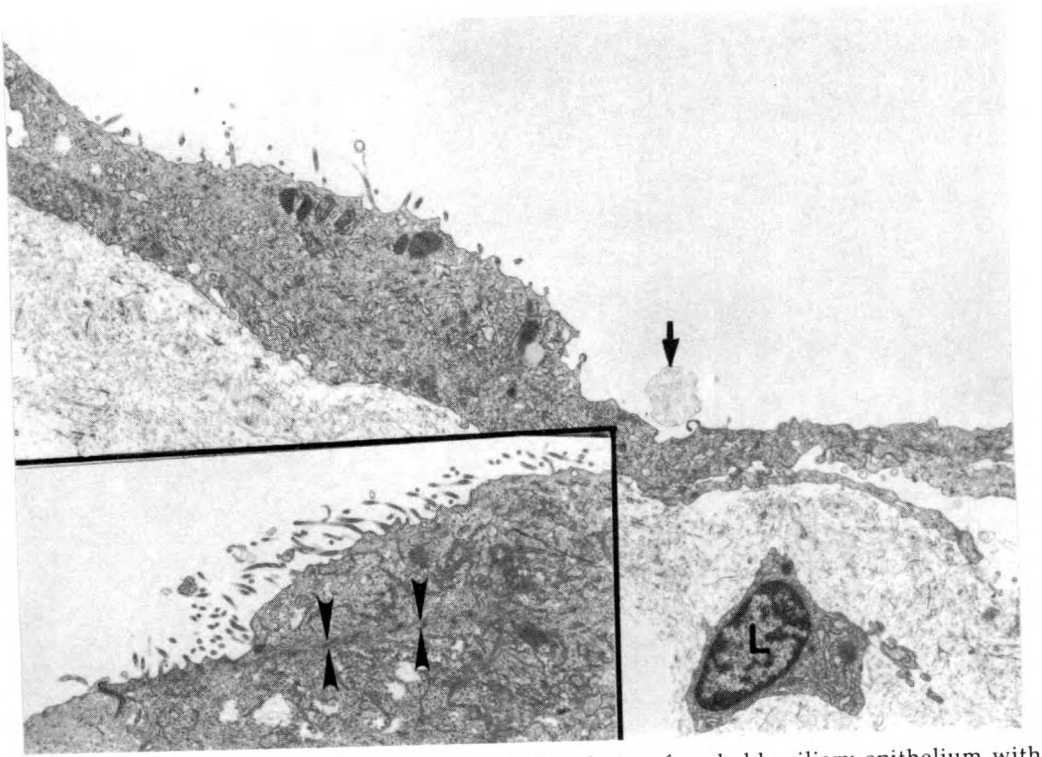


Fig. 2 (Lopez and associates). Vitrectomy specimen. Monolayer of probable ciliary epithelium with surface microvillus processes, abundant intracytoplasmic endoplasmic reticulum, associated membrane bound vacuoles (arrow), and subplasmalemmal filaments with focal densities (inset, between arrowheads) suggestive of myofibroblastic differentiation overlies collagen fibrils and a lymphoplasmacytoid cell (L) (×8,120; inset, ×8,120).

tural finding specific for posterior proliferative vitreoretinopathy was the presence of retinal internal limiting membrane fragments. Internal limiting membrane fragments were present in four posterior proliferative vitreoretinopathy specimens.

Enucleated eyes—The clinical findings of the patients with anterior proliferative vitreoretinopathy, rhegmatogenous retinal detachment, and hypotony who underwent enucleation are listed in Table 3. The mean age of the ten patients whose enucleated eyes were studied was 55.7 years. Six patients were female and four were male. Nine eyes had previous cataract extraction: four were extracapsular, one was intracapsular, and four were unspecified. Four eyes had intraocular lens implants and five eyes were aphakic. Seven eyes had a history of previous surgery for retinal detachment including six with scleral buckling procedures alone and one with a pars plana vitrectomy alone. No giant retinal tears were noted in any of the enucleated eyes. There was no history or evidence of trauma in any eye other than previous surgery for cataract or retinal detachment. All eyes had been enucleated because of visual acuity of no light perception and pain.

The histopathologic, immunohistochemical, and ultrastructural features of the ten enucleated eyes with anterior proliferative vitreoretinopathy and chronic hypotony are summarized in Table 4. In these eyes, tractional membranes extended from the peripheral retina, vitreous base, and pars plana, and attached to the pars

Fig. 1 (Lopez and associates). Vitrectomy specimen. Anterior proliferative vitreoretinopathy membrane with incorporated ciliary epithelium. Top, Probable ciliary epithelium (CE) separated by a layer of basement membrane (arrowheads) from a membrane composed of fibrocytes (FIB), collagen bundles (arrow), and fibrin (asterisk) in a surgically removed anterior proliferative vitreoretinopathy membrane. A cilium (curved arrow) is present in the cytoplasm of one cell (×8,700). Bottom, Corresponding diagram demonstrates sheet of ciliary epithelium adjacent to fibrocellular membrane.

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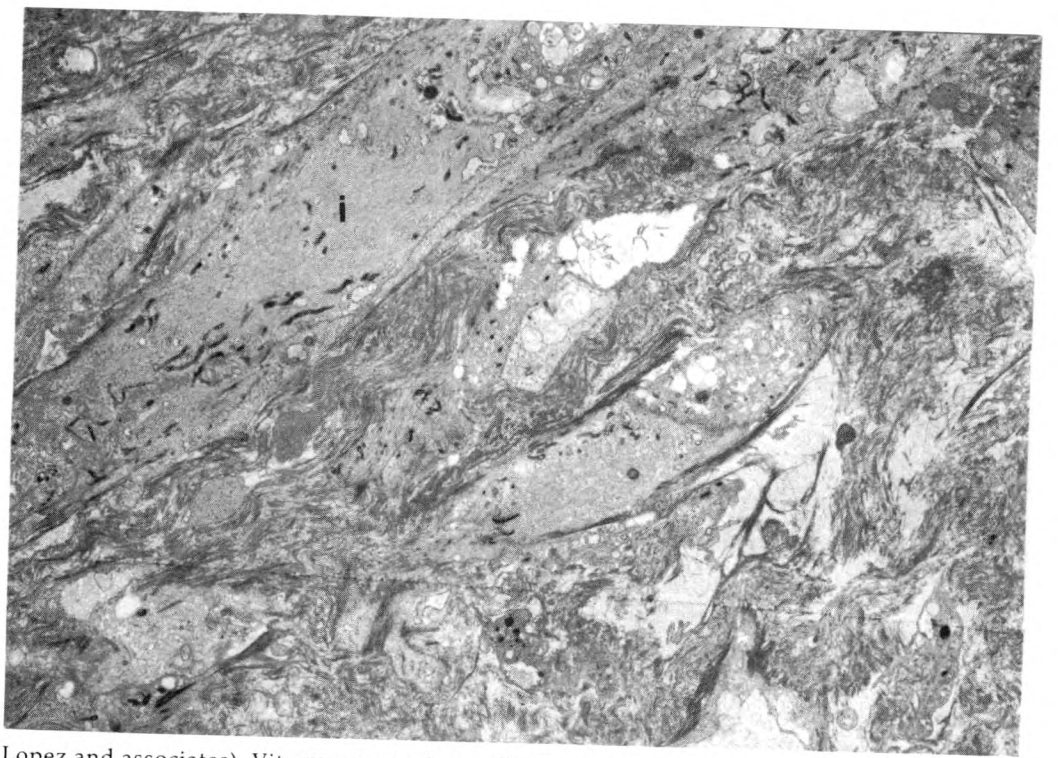


Fig. 3 (Lopez and associates). Vitrectomy specimen. Glial cells that are elongated and contain numerous 8- to 10-nm intracytoplasmic intermediate filaments (i) are surrounded by collagen fibrils and degenerated material (× 1,900).

plicata of the ciliary body, the posterior surface of the iris, or the pupillary margin. In all ten eyes, a condensed, contracted vitreous base produced traction on the peripheral retina and ciliary body and provided a scaffold for the proliferation of cellular components derived from either the tractional membrane or surrounding ocular structures.

The histopathologic findings in the anterior proliferative vitreoretinopathy of the enucleated eyes could be classified according to three stages: traction (Fig. 5), incorporation (Fig. 6), and proliferation (Fig. 7). Intermediate or transitional stages were also present. In the traction stage (Fig. 5), fibrocellular contraction of the vitreous base resulted in detachment of the peripheral retina and the nonpigmented epithelium of the pars plana of the ciliary body. This detachment resulted in the formation of a circumferential trough that was lined on one side by anteriorly displaced undulating folds of retina and on the other side by components of the pars plana, the pars plicata of the ciliary body, or both. The traction stage represented the stage with the least contraction and cellular proliferation into the vitreous base and was associated with the widest circumferential

TABLE 3
CLINICAL FEATURES IN TEN PATIENTS WITH EYES ENUCLEATED WITH ANTERIOR PROLIFERATIVE VITREORETINOPATHY

CASE NO., AGE (YRS), GENDER	EYE	PREDISPOSING FACTOR	PRIOR RETINAL SURGERY
1, 65, M	R.E.	Intracapsular cataract extraction	None
2, 65, F	R.E.	Extracapsular cataract extraction with intraocular lens implant	Pars plana vitrectomy
3, 42, M	R.E.	Cataract extraction	None
4, 41, F	L.E.	Cataract extraction; retinal detachment since childhood	None
5, 48, F	R.E.	Extracapsular cataract extraction with intraocular lens implant	Scleral buckle twice
6, 69, F	L.E.	Extracapsular cataract extraction with intraocular lens implant	Scleral buckle
7, 12, M	L.E.	Cataract extraction	Scleral buckle and vitrectomy
8, 62, F	L.E.	Cataract extraction	Scleral buckle
9, 23, M	R.E.	Cataract extraction	Scleral buckle
10, 90, F	L.E.	Extracapsular cataract extraction	Scleral buckle

TABLE 4
HISTOLOGIC, IMMUNOHISTOCHEMICAL, AND ULTRASTRUCTURAL FINDINGS IN TEN ENUCLEATED EYES WITH ANTERIOR PROLIFERATIVE VITREORETINOPATHY

	NO. OF EYES
Histologic Findings	
Condensed vitreous	10
Tears of pars plana epithelium	10
Tears of pars plicata epithelium	10
Fibrovascular ingrowth from uvea or retina	10
Nonpigmented ciliary epithelium hyperplasia	9
Pigment epithelium proliferation	9
Glial proliferation	8
Lens remnants	7
Fibrous ingrowth from cataract wound	2
Immunohistochemical findings	
Ulex europaeus	10
S-100 protein	5
Leukocyte common antigen	4
Glial fibrillary acid protein	3
Neuron specific enolase	0
Ultrastructural findings	
Ciliary body epithelium	8
Fibrous astrocytes	2
Fibrocytes	4
Macrophages	4
Lymphocytes	2
Myofibroblasts	1
Endothelium-lined vascular channels	3
Erythrocytes	3
Plasma cells	1
Polymorphonuclear leukocytes	1
Original collagen	6
New collagen	4

troughs and the least anterior dragging of the peripheral retina. The tractional effects on the pars plicata of the ciliary body in this stage resulted in focal areas of nonpigmented ciliary epithelium hyperplasia, particularly at the tips of the ciliary processes. Tearing or avulsion of small areas of nonpigmented and occasionally pigmented ciliary epithelium resulted in focal areas of ciliary epithelial rarefaction or denudation along the ciliary processes. Nonpigmented ciliary epithelium hyperplasia of the pars plicata was present in nine of the enucleated eyes. Multifocal avulsions and tears of the ciliary epithelium of the pars plicata were present in all ten eyes. In five of the ten enucleated eyes, separation or detachment of the ciliary body was present; however, none of these eyes contained serous fluid in the supraciliary space. No cyclodialysis was present in any eye.

Progressive fibrocellular contraction resulted in the incorporation stage that was associated with tears within both the ciliary body and retina. In this stage, torn fragments of the ciliary epithelium from both the pars plana and pars plicata as well as retinal fragments became enmeshed (incorporated) within the circumferential trough formed by the contracted vitreous base (Fig. 6). This stage was associated with further narrowing of the width of the circumferential trough and more severe anterior dragging of the detached peripheral retina. Cystic spaces lined by dialyzed peripheral retina and ciliary epithelium as well as areas of tears of the ciliary epithelium from the ciliary processes first appeared during this stage. Other components that became incorporated into anterior proliferative vitreoretinopathy included lens remnants in seven eyes, intraocular lens haptics in six, and iris fragments in one.

The third stage of anterior proliferative vitreoretinopathy in the enucleated eyes was the proliferation stage. This stage was characterized by fibrovascular ingrowth (neovascularization) from the uvea, retina, or both, into the vitreous base (Fig. 7). Although fibrovascular ingrowth was histologically found to some degree in all ten eyes, it was most prominent in the proliferation stage. The most narrow circumferential troughs and the most severe anterior dragging of the peripheral retina were found in this stage. Small areas of ciliary epithelium and retinal glial cell proliferation were present to some degree in up to nine of the enucleated eyes (Table 4); however, marked cellular proliferation and fibrovascular ingrowth from the retina, uvea, or both, were present only in the proliferation stage. Proliferated pigmented or nonpigmented epithelium cells occasionally formed nodular (Fig. 7), acinar, or tubuloacinar patterns within the anterior proliferative vitreoretinopathy. Glial cell proliferation from the anterior retinal surface was present in eight of the ten enucleated eyes. The proliferating glial cells were exclusively incorporated into membranes formed by other cellular components, particularly pigmented and nonpigmented epithelium cells. Fibrovascular ingrowth into the vitreous base from the peripheral retina, the ciliary stroma, or both, through breaks in the ciliary epithelium, was noted in all ten enucleated eyes. Conversely,

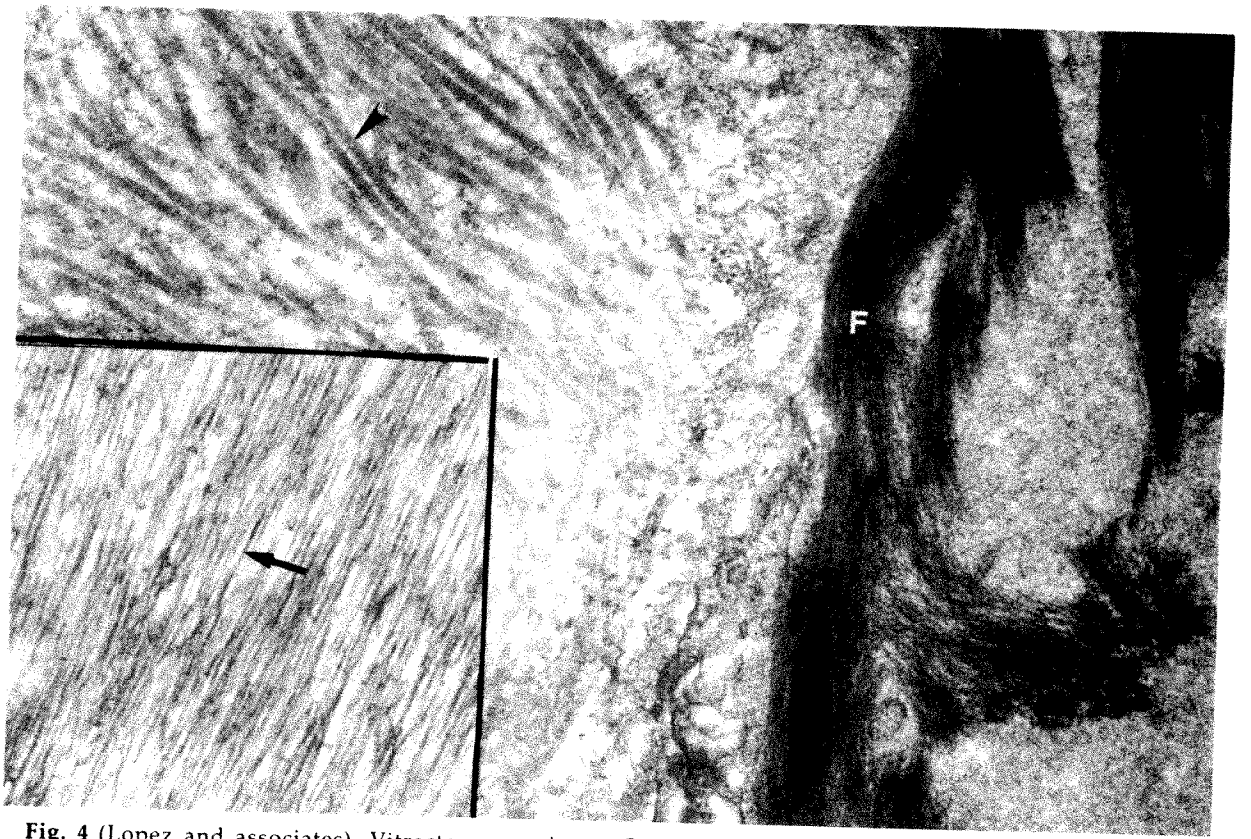


Fig. 4 (Lopez and associates). Vitrectomy specimen. Original vitreous collagen, new collagen, and fibrin. Original collagen fibrils (inset, arrow) measuring up to 15 nm in diameter, new collagen fibrils (arrowhead) measuring up to 250 nm in diameter, and fibrin (F) present in the extracellular matrix of an anterior proliferative vitreoretinopathy membrane (× 8,700; inset, × 8,700).

fibrovascular ingrowth from the iris stroma into the anterior proliferative vitreoretinopathy was not found in any eye. Fibrous ingrowth from prior corneoscleral cataract incisions was present in two of the ten eyes.

Immunohistochemical analysis of the anterior proliferative vitreoretinopathy in the enucleated eyes was performed in order to define the cell types involved better. *Ulex europaeus* agglutinin, a fucose-binding lectin that is a marker for human vascular endothelium,[19] was found in all ten eyes (Fig. 8). The S-100 protein, a marker for cells of neuroectodermal origin, including ciliary body epithelium[20-22] and glial cells,[20] was present in cells within the anterior proliferative vitreoretinopathy in 50% of the eyes (Fig. 9). Because all the cells that stained for S-100 protein failed to stain for glial fibrillary acid protein, these cells were interpreted as representing ciliary epithelium. The leukocyte common antigen, a general marker for inflammatory cells including lymphocytes, macrophages, polymorphonuclear leukocytes, and plasma cells,[23] was noted in four of the ten eyes. Glial fibrillary acid protein, an intermediate cytoplasmic filament characteristically present in glial cells,[20] was found in three of the eyes. Neuron-specific enolase, a glycolytic isoenzyme present in cells of neuronal or neuroendocrine lineage including photoreceptor cells,[20] was not detected in any specimen.

Electron microscopy of the anterior proliferative vitreoretinopathy in the enucleated eyes was performed in order to correlate the ultrastructural findings in the enucleated eyes with those of the vitreous biopsy specimens. Ciliary body epithelium was present in eight of the ten eyes and was the principal cell type found in the anterior proliferative vitreoretinopathy. Other structural cellular components included fibrocytes in four eyes and fibrous astrocytes in two. Myofibroblasts, suggestive of active con-

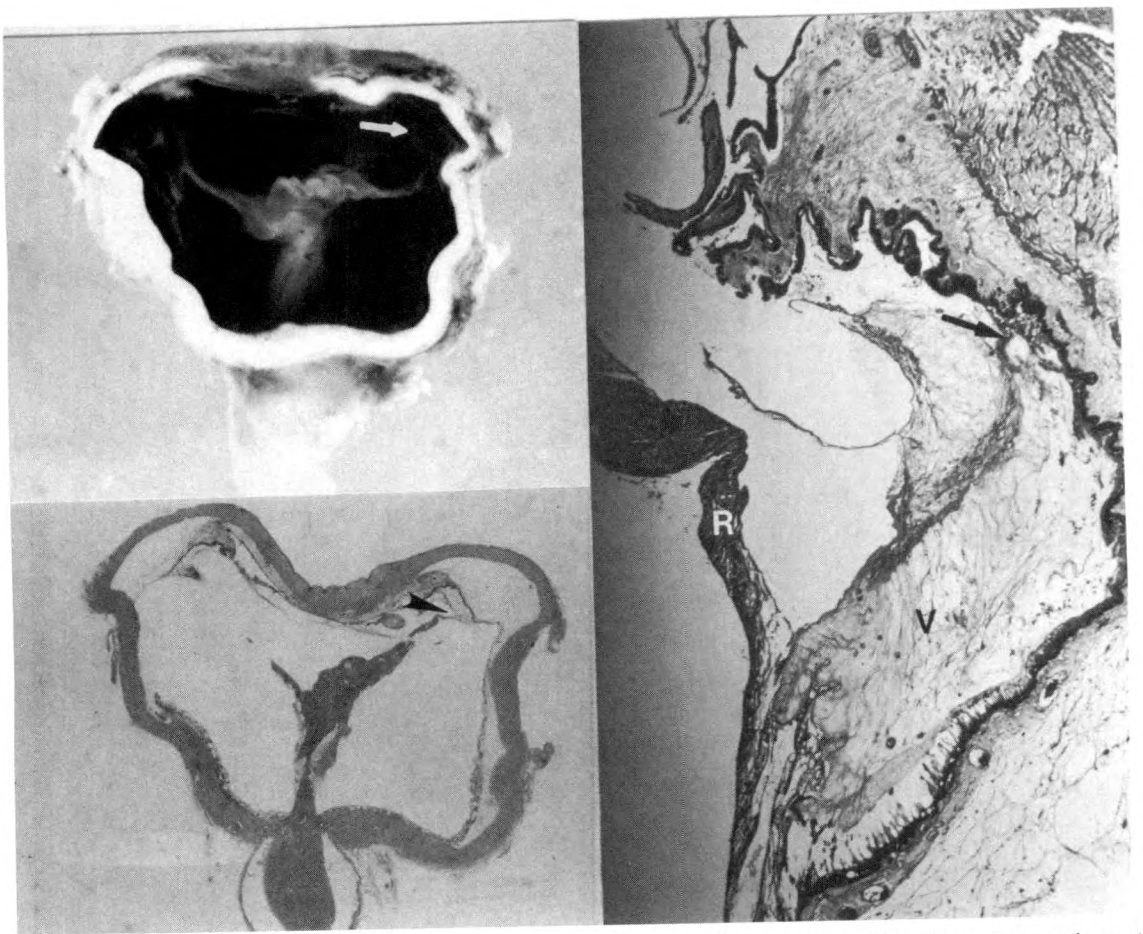


Fig. 5 (Lopez and associates). Enucleation specimen. Traction stage in anterior proliferative vitreoretinopathy. Top left, Gross photograph of an eye with anterior proliferative vitreoretinopathy shows a funnel-shaped retinal detachment with traction in the area of the vitreous base (arrow). Bottom left, Low-power photograph of corresponding histologic section shows a trough between the peripheral retina and ciliary body (arrowhead) (hematoxylin and eosin, × 2). Right, Closer inspection of the area indicated by the arrow and arrowhead in the photographs on the left shows traction of the vitreous base (V) on ciliary nonpigmented epithelium (arrow) and detached retina (R) (hematoxylin and eosin, × 125).

traction within the anterior proliferative vitreoretinopathy, were found in one of the eyes. The ultrastructural features of fibrovascular ingrowth from the retina, the uvea, or both, included endothelium-lined vascular channels with erythrocytes in three. Vascular channels in anterior proliferative vitreoretinopathy were better demonstrated histologically and by immunohistochemical staining for *Ulex europaeus* than by ultrastructural examination. Perhaps this was because the vessels were more prominent and easily sampled for electron microscopy only in the advanced (proliferation) stage. Inflammatory cells were frequently present within the stroma of the anterior proliferative vitreoretinopathy and in general were not directly associated with the endothelium-lined vascular channels. Macrophages were the predominant inflammatory cell type found within the anterior proliferative vitreoretinopathy. Other inflammatory cells included lymphocytes in two eyes, plasma cells in one, and polymorphonuclear leukocytes in one. Both original vitreous collagen in six eyes and new collagen in four eyes were present in the anterior proliferative vitreoretinopathy of the enucleated eyes. In some eyes, there was a parallel arrangement of the collagen bundles within the ante-

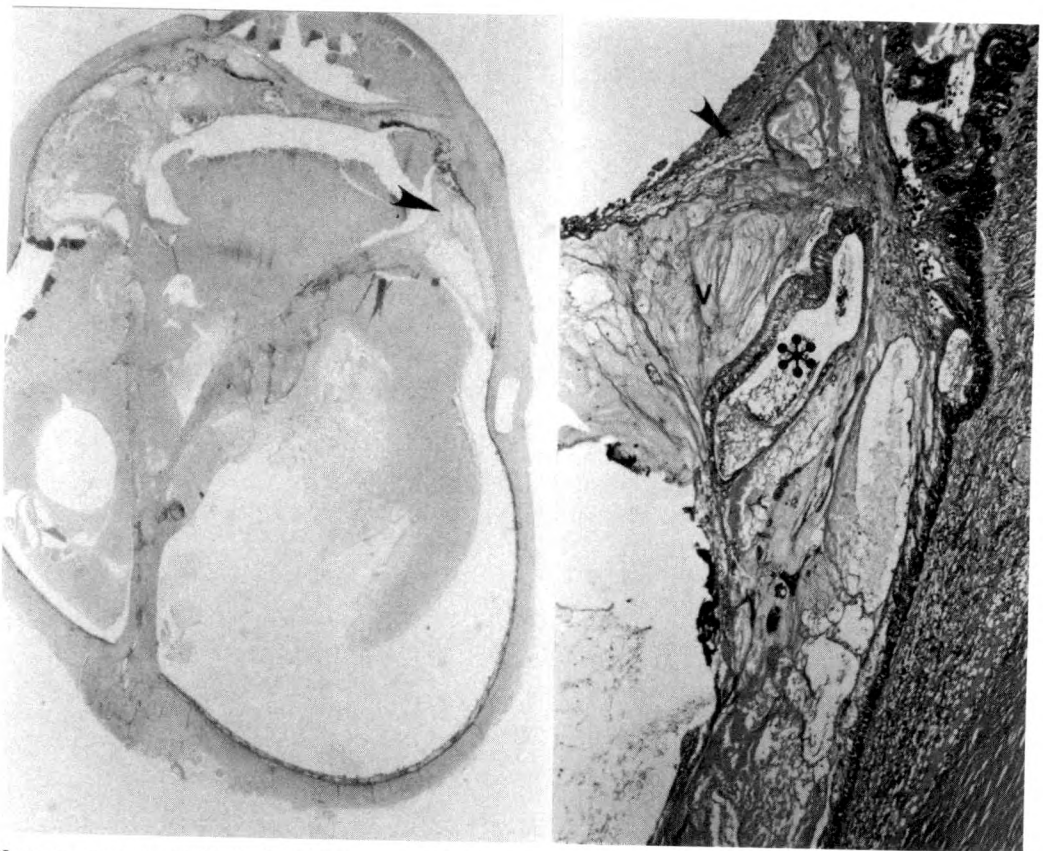


Fig. 6 (Lopez and associates). Enucleation specimen. Incorporation stage in anterior proliferative vitreoretinopathy. Left, An eye after retinal detachment repair with a persistent retinal detachment has developed anterior proliferative vitreoretinopathy (arrowhead) (hematoxylin and eosin, × 4). Right, Area corresponding to arrowhead in photograph on the left shows a fibrocellular membrane (arrowhead) on the surface of the contracted vitreous base (V) that has incorporated a cyst (asterisk) lined by dialyzed peripheral retina/ciliary epithelium, which has become incorporated into the anterior proliferative vitreoretinopathy (hematoxylin and eosin, × 125).

rior proliferative vitreoretinopathy (Fig. 10), suggestive of tangential traction.

Discussion

Proliferative vitreoretinopathy appears to be an extension of the physiologic reparative wound healing response to retinal detachment. Unfortunately, this process may lead to failure of otherwise successful surgical retinal reattachment.[1,2] Two types of proliferative vitreoretinopathy have been defined by their anatomic location in relation to the posterior insertion of the vitreous base: anterior proliferative vitreoretinopathy and posterior proliferative vitreoretinopathy.[3-6] Both disorders are initiated by the same reparative fibrocellular proliferation. Divergence in the evolution of anterior from posterior proliferative vitreoretinopathy occurs secondary to the tractional effects of the initial fibrocellular proliferation on adjacent anterior ocular tissues such as the iris, ciliary body, and peripheral retina. This divergence may result in the incorporation and proliferation of components of these anterior ocular tissues into the fibrocellular proliferation within the vitreous base in anterior proliferative vitreoretinopathy.

The histopathologic, ultrastructural, and immunohistochemical findings in the ten enucleated eyes examined in this study suggest that

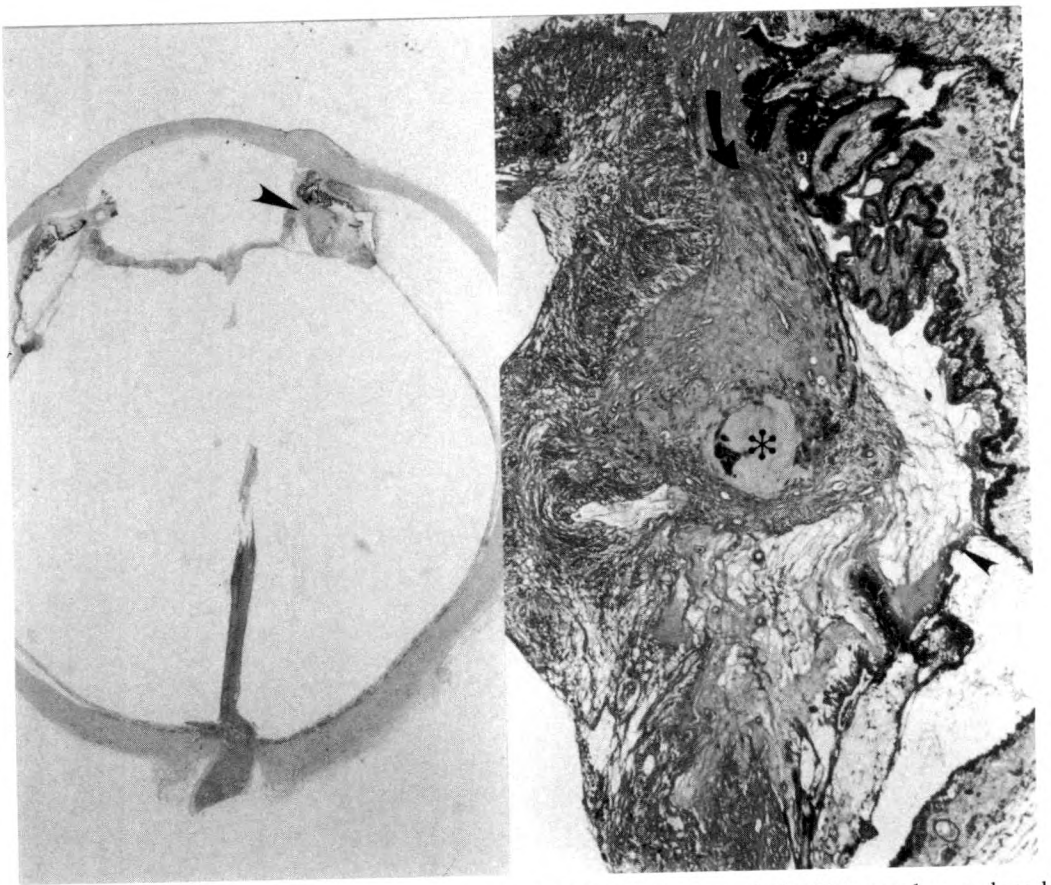


Fig. 7 (Lopez and associates). Enucleation specimen. Proliferation stage. Left, This eye has a closed, totally detached retina drawn forward by anterior proliferative vitreoretinopathy (arrowhead) (hematoxylin and eosin, × 4). Right, Area corresponding to arrowhead in photograph on left shows vitreous base with incorporated, proliferated ciliary body epithelium (curved arrow), some of which is in a nodular configuration (asterisk), that causes traction on the detached retina and sheet of ciliary body nonpigmented epithelium (arrowhead) (hematoxylin and eosin, × 125).

the pathogenetic evolution of anterior proliferative vitreoretinopathy occurs in three consecutive stages: traction, incorporation, and proliferation. The three stages are a continuum of events and therefore intermediate and transitional stages also exist. In the traction stage, fibrocellular contraction of the vitreous base results in detachment of the peripheral retina and the nonpigmented ciliary epithelium of the pars plana (Fig. 5). Clinically, this detachment is manifest as a circumferential trough lined on one side by anteriorly displaced undulating folds of retina and on the other side by components of the pars plana, the pars plicata of the ciliary body, or both. In this stage, tractional effects on the pars plicata of the ciliary body may occur and result in focal, multifocal, or diffuse areas of nonpigmented ciliary epithelium hyperplasia, particularly at the tips of the ciliary processes (Figs. 9 and 10), and tearing or avulsion of small focal or multifocal areas of nonpigmented and occasionally pigmented ciliary epithelium. This stage results in denudation of the ciliary processes and breakdown of the ciliary blood aqueous barrier. Some of these findings are similar to those seen in other eyes with cyclitic membranes such as those with pars planitis.[24,25] Progressive fibrocellular contraction results in the incorporation stage, which is characterized by tears with combined traction and rhegmatogenous detachment of both the ciliary body and retina (Fig. 6). In this

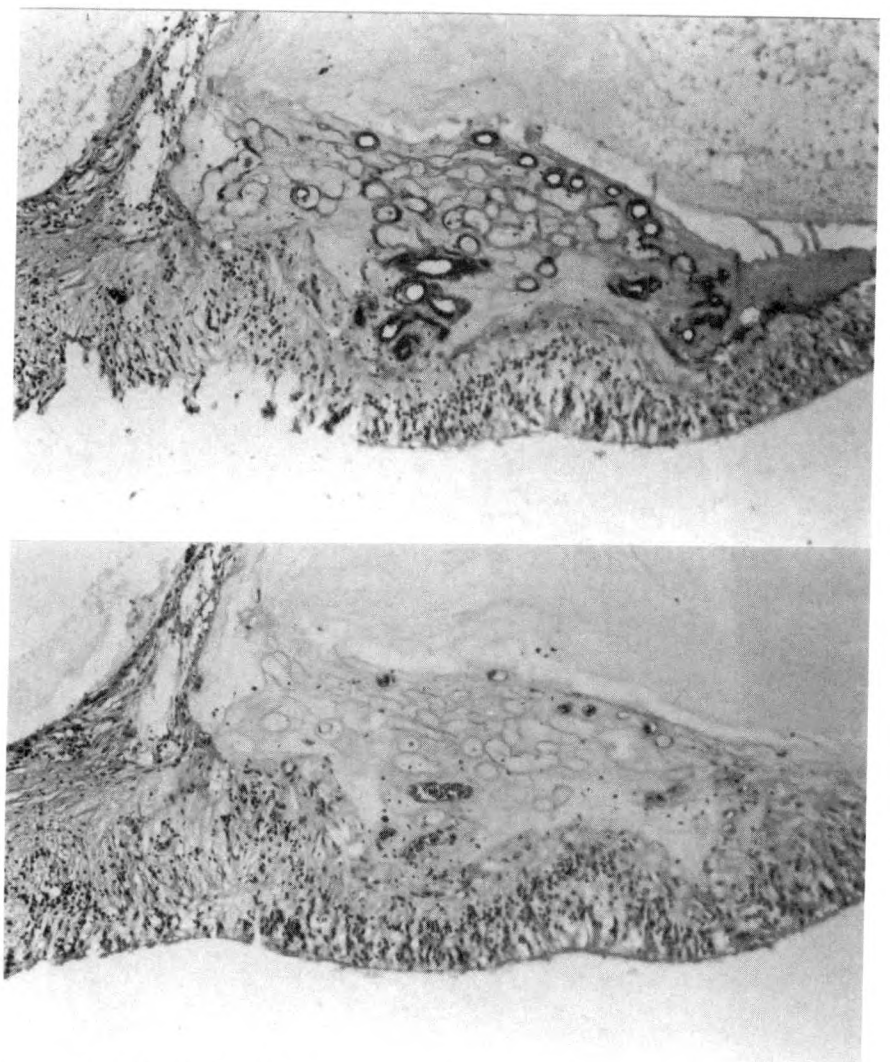


Fig. 8 (Lopez and associates). Enucleation specimen. Top, Staining of vascular endothelium with *Ulex europaeus* agglutinin shows the neovascularization in the anterior proliferative vitreoretinopathy to have originated from the retina in an enucleated eye. Bottom, A control fails to stain (peroxidase antiperoxidase, × 25).

stage, an aggregation of torn fragments of the ciliary epithelium, from both the pars plana and pars plicata, and retinal fragments become enmeshed within the circumferential trough formed by the contracting vitreous base. Lens remnants, intraocular lens haptics, and iris fragments also become incorporated into the anterior proliferative vitreoretinopathy during this stage. Each of these structures may serve as both a scaffold for further cellular proliferation and as an anchor for anterior displacement of the vitreous base during active contraction.

The third stage in the evolution of anterior proliferative vitreoretinopathy consists of proliferation of the incorporated tissues (Fig. 7) and fibrovascular ingrowth (neovascularization) from the uvea, retina, or both (Fig. 8). Each of these proliferative tissues may contribute to further contraction of the anterior proliferative vitreoretinopathy with progressive damage to the ciliary body and other anterior segment structures. In general, as the stages of the anterior proliferative vitreoretinopathy were more advanced, the circumferential

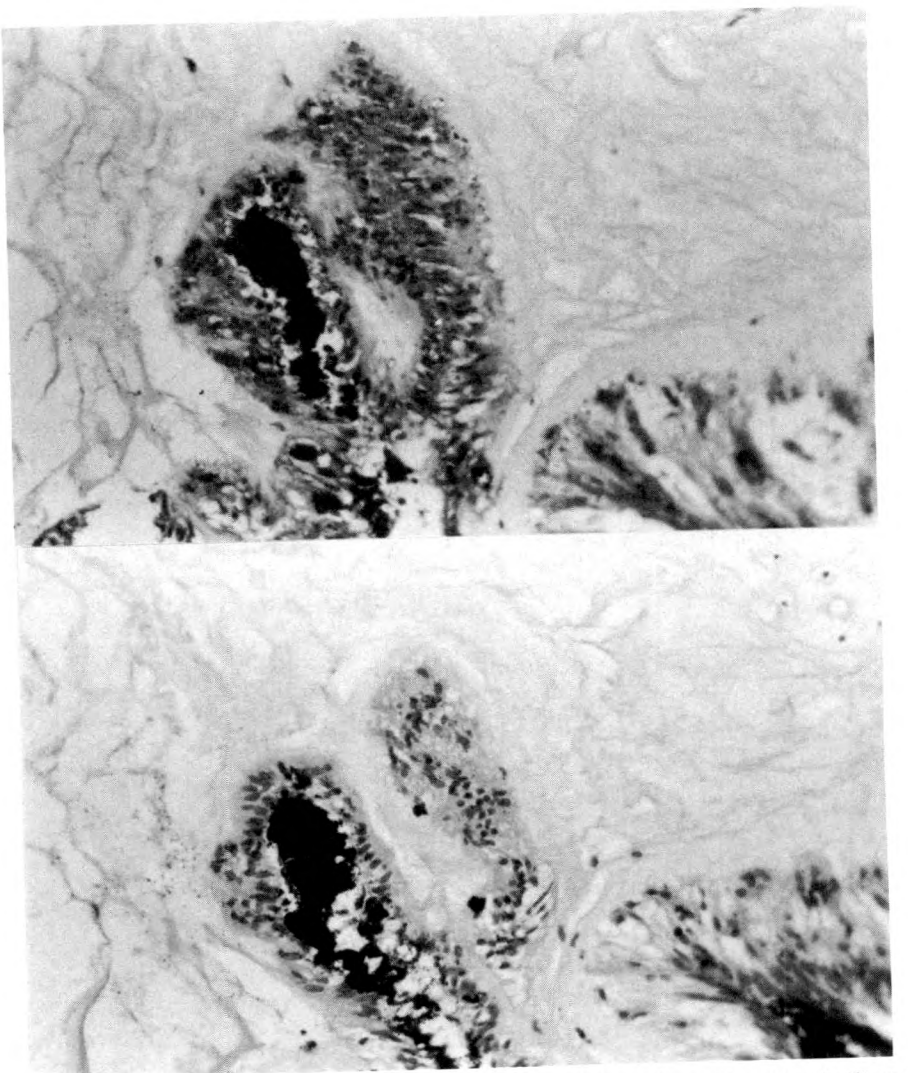


Fig. 9 (Lopez and associates). Enucleation specimen. Positive staining of nonpigmented ciliary epithelium for S-100 protein in anterior proliferative vitreoretinopathy can be appreciated when comparing the stained slide (top) with the control (bottom) (peroxidase antiperoxidase, × 63).

trough was longer and narrower, the peripheral retina was more anteriorly dragged, and the membranes were more opaque. These findings are consistent with progressive fibrocellular proliferation and contraction.

The ultrastructural features of ten surgically excised anterior proliferative vitreoretinopathy membranes differed from those of posterior proliferative vitreoretinopathy coexisting in the same eye (Table 2). Nonpigmented and pigmented ciliary body epithelium were the principal cell types present in surgically excised anterior proliferative vitreoretinopathy membranes; whereas, surgically excised posterior proliferative vitreoretinopathy membranes were characterized by a predominance of retinal pigment epithelium, fibrocytes, and macrophages. Ultrastructural findings that were present only in surgically excised anterior proliferative vitreoretinopathy membranes included, in decreasing order of frequency, nonpigmented and pigmented ciliary body epithelium, endothelium-lined vascular channels, and fibrin. The presence of internal limiting membrane was the only specific ultrastructural feature of the surgically excised posterior prolif-

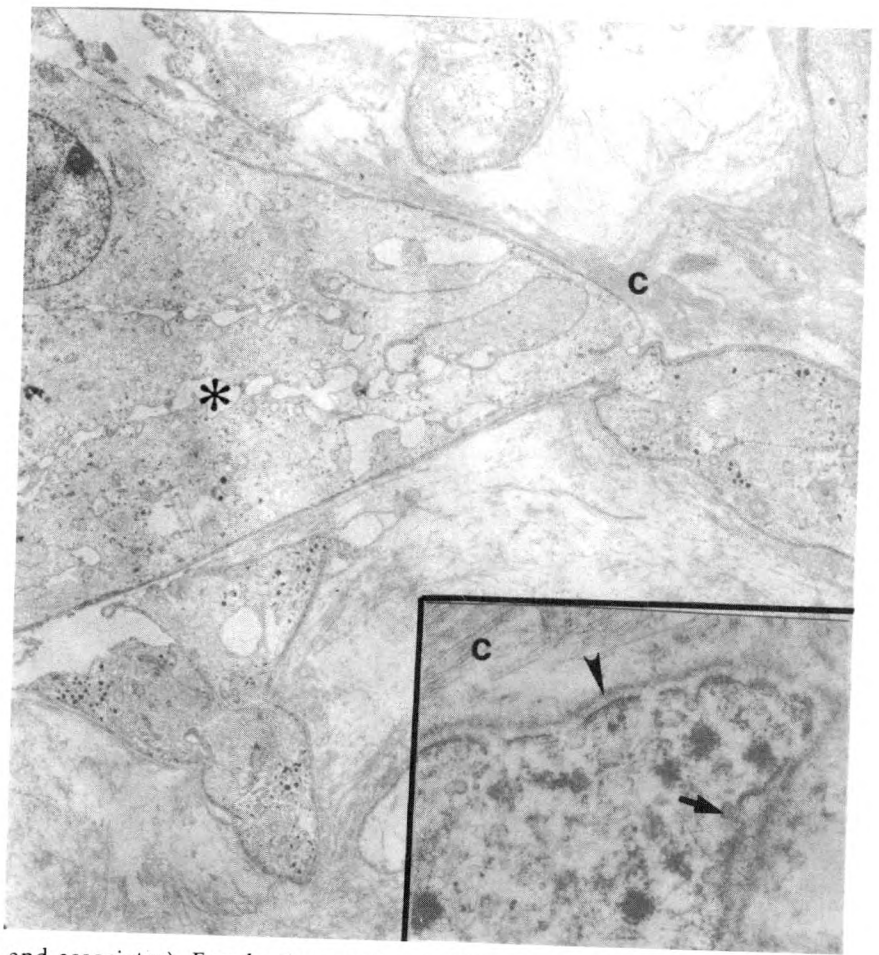


Fig. 10 (Lopez and associates). Enucleation specimen. Ultrastructural examination of anterior proliferative vitreoretinopathy in an enucleated eye shows a sheet of nonpigmented ciliary epithelium forming an acinar structure (asterisk) with adjacent collagen fibrils (C) parallel to the plasma membrane of the epithelium. Inset, Higher magnification discloses the intimate relationship between the collagen fibrils (C) and the basement membrane (arrowhead) of the ciliary epithelium. The ciliary epithelium exhibits micropinocytic vesicle formation (arrow) (uranyl acetate and lead citrate, ×3,420; inset, ×25,200).

erative vitreoretinopathy membranes. These findings reflected both differences in the composition of anterior and posterior proliferative vitreoretinopathy, as well as the effects of current vitreous surgical techniques used in their excision.

The features of the surgically excised anterior proliferative vitreoretinopathy membranes examined in this study differ from those previously described.[7] In the report by Elner and associates,[7] the ultrastructural features of seven surgically excised anterior proliferative vitreoretinopathy membranes were described as typical of posterior proliferative vitreoretinopathy and included glial cells, fibroblasts, myofibroblasts, and pigment-laden cells, some of which had the morphologic features of macrophages. It is unclear whether the discordant findings between that report[7] and those of our study represent differences in case selection (all of our patients had severe anterior proliferative vitreoretinopathy with hypotony and eyes with previous trauma were excluded), differences in surgical biopsy techniques, or differences in pathologic classification (perhaps some of the pigment-laden cells in the previous report[7] were ciliary epithelium). Our findings, however, are similar to those of Zarbin, Michels, and Green[12] who performed epiciliary membrane dissection in eyes with chronic hypotony after surgery for proliferative vitreoretinopathy. The histopathologic findings in the enucleated eyes

with anterior proliferative vitreoretinopathy in our study are in agreement with those of Elner and associates.[7] Additionally, the ultrastructural features of the surgically excised posterior vitreoretinopathy in our study are concordant with previous reports of similar membranes.[26-29]

The clinicopathologic findings in the ten patients who underwent vitrectomy and dissection of anterior proliferative vitreoretinopathy provided insight into the pathogenetic mechanisms of chronic hypotony that occurs in some eyes with anterior proliferative vitreoretinopathy[8-12] and of the postvitrectomy fibrin syndrome in some of these eyes.[13] All ten eyes that underwent retinal reattachment surgery with dissection of anterior proliferative vitreoretinopathy had low preoperative ocular tensions (10 mm Hg or less). Seven of the ten eyes had chronic preoperative hypotony, defined as ocular tension of 5 mm Hg or less on two or more different examinations at least one month apart. Possible pathogenetic mechanisms of low preoperative ocular tension or chronic hypotony in these eyes included at least two mechanisms. One may be increased aqueous outflow through either a cyclodialysis cleft, serous choroidal detachment,[12] or open breaks in the retina, ciliary epithelium, or both. Another mechanism may be decreased aqueous production secondary to ciliary body dysfunction caused directly by ischemic necrosis of the ciliary body caused by choroidal vascular congestion and stasis, indirectly by cryotherapy, photocoagulation, or an encircling scleral buckle,[12] or by the tractional effects of epiciliary membranes on the pars plicata. None of the eyes examined in this study had a cyclodialysis cleft detectable either by careful preoperative or postoperative gonioscopy or by intraoperative examination of the anterior chamber angle by contact lens biomicroscopy with limbal indentation. Likewise, serous choroidal detachment was not detected ophthalmoscopically or echographically in any eye.

Increased aqueous outflow through open breaks in the retina, ciliary epithelium, or both, is a potential mechanism of hypotony in eyes with anterior proliferative vitreoretinopathy. Retinal breaks that were fixed open by anterior or posterior proliferative vitreoretinopathy, or both, were identified preoperatively or intraoperatively in eight of the ten eyes. These open, fixed retinal breaks included large flap tears in four eyes and a giant retinal tear in one eye. All of the visible retinal breaks were located at or posterior to the posterior insertion of the vitreous base. Two eyes with identifiable open, fixed retinal breaks had multiple, small, aphakic or pseudophakic flap tears at the posterior margin of the vitreous base insertion.

In two eyes with rhegmatogenous retinal detachment and anterior proliferative vitreoretinopathy, no identifiable open retinal breaks were found during either preoperative or intraoperative examination. These eyes were presumed to have one of several possibilities. Multiple, undetected, small retinal breaks in the tractionally thinned retina along the posterior margin of the vitreous base insertion may have been present. Tractionally open tears in the retina or ciliary epithelium of the pars plana (especially along the anterior border of the vitreous base insertion) that were clinically obscured by overlying opaque anterior proliferative vitreoretinopathy membranes may have occurred. Alternatively, fixed breaks in the ciliary body pars plicata that were obscured may have been clinically undetected. Similar ciliary breaks have been associated with rhegmatogenous retinal detachment in other conditions.[30-34]

Tractionally open anterior retinal or ciliary tears, or both, that were obscured by overlying membranes not only explain the occurrence of rhegmatogenous retinal detachments in some eyes with anterior proliferative vitreoretinopathy without clinically identifiable retinal breaks, but also may in some cases provide potential sites of increased aqueous outflow through either the ciliary body or the choroid. All three eyes with low preoperative ocular tensions of 5 to 10 mm Hg and three of the seven eyes with chronic preoperative hypotony (5 mm Hg or less) recovered postoperative ocular tensions of 10 mm Hg or greater after retinal reattachment with closure of the retinal or ciliary epithelial breaks, or both (Table 1). In all of those eyes, meticulous dissection of the anterior proliferative vitreoretinopathy was necessary to achieve intraoperative retinal reattachment. This dissection often required extensive, circumferential excision of the tractionally detached pars plana ciliary epithelium. Because these eyes regained a normal postoperative ocular tension (10 mm Hg or greater), our findings suggest that extensive surgical excision of the nonpigmented pars plana ciliary epithelium does not by itself result in chronic hypotony. Disruption of the ciliary blood-aqueous barrier induced by this surgical maneuver may, however, increase the incidence of postvitrectomy fibrin syndrome.

Tractional dehiscence of the cilioretinal sym-

physis[35] from the underlying pigment epithelium at the ora serrata was present in most of the eyes with anterior proliferative vitreoretinopathy that were studied clinically or pathologically and may have contributed to hypotony. A similar dehiscence of the cilioretinal symphysis secondary to vitreous traction associated with localized detachment of the nonpigmented pars plana ciliary epithelium has been reported primarily in the superior quadrants of some eyes with idiopathic rhegmatogenous retinal detachments.[36] In the vitrectomy cases in our study, tractional detachment of the vitreous base with secondary dehiscence of the cilioretinal symphysis from the underlying pigment epithelium was often present along the entire circumferential extent of the anterior proliferative vitreoretinopathy, but was most common in the inferior quadrants. In these eyes, tractional dehiscence of the cilioretinal symphysis appeared to occur primarily as a result of fibrocellular contraction of the vitreous base. However, a contribution from previous surgical trauma cannot be excluded in those eyes that had prior vitrectomy or cataract extraction with vitreous loss. In any event, dehiscence of the cilioretinal symphysis provides access of subciliary epithelium fluid to the subretinal space and may in part explain the mechanism of rhegmatogenous retinal detachment in such eyes with tractionally open ciliary breaks, as well as possibly contribute to the mechanism of increased aqueous outflow in similar eyes with low ocular tension or hypotony. Greater forward displacement of the vitreous base, after dehiscence of the cilioretinal symphysis, may also facilitate adhesion of residual vitreous, membranes, or both, to the pars plicata ciliary epithelium, promoting the development of chronic intractable hypotony. Functional closure of ciliary epithelium, undetected retinal tears, or both, as well as reestablishment of a functional cilioretinal symphysis, was accomplished by scatter endophotocoagulation on an encircling scleral buckle in the study eyes.[6,37]

Another potential mechanism of hypotony in eyes with anterior proliferative vitreoretinopathy is traction detachment of the ciliary body. This may be associated with serous supraciliary effusion, resulting in impaired aqueous secretion or increased uveoscleral outflow. Surgical dissection of the anterior proliferative vitreoretinopathy in some such eyes may relieve the traction detachment of the ciliary body and restore normal ocular tension. Traction detachment of the ciliary body was not detected in any of the ten eyes studied clinically. Separation or detachment of the ciliary body was present in some of the ten enucleated eyes with anterior proliferative vitreoretinopathy and hypotony. In these eyes, no histopathologically identifiable supraciliary exudate was found. It is unclear whether separation of the ciliary body in some of the enucleated eyes in our series represented a histopathologic processing artifact or true detachment of the ciliary body.

Four of the seven eyes with preoperative hypotony (5 mm Hg or less) remained hypotonus postoperatively (Table 1), despite closure of the retinal or ciliary epithelium breaks, or both, and excision of the anterior proliferative vitreoretinopathy. Overall, success with regard to hypotony was achieved in three of seven eyes. These results are comparable with those of Zarbin, Michels, and Green[12] who found that four of nine eyes with preoperative hypotony regained a normal ocular tension of 10 mm Hg or greater postoperatively after epiciliary dissection. To define better the mechanism responsible for the persistent postoperative hypotony, a multivariate analysis of the preoperative and intraoperative clinical findings was performed. Two preoperative clinical variables appeared uniformly predictive of chronic postoperative hypotony (5 mm Hg or less) despite successful retinal reattachment and excision of the anterior proliferative vitreoretinopathy. These variables were (1) striate keratopathy without corneal epithelial edema; and (2) a circumferential ring of opaque, white, fibrous, anterior proliferative vitreoretinopathy that extended and attached either at or anterior to the pars plicata of the ciliary body.

Striate keratopathy in the eyes with anterior proliferative vitreoretinopathy and hypotony is a manifestation of corneal endothelium dysfunction and may be secondary to previous surgical trauma or to ciliary body dysfunction, resulting in impaired aqueous secretion and endothelium malnutrition. In general, the eyes with anterior proliferative vitreoretinopathy and striate keratopathy had a similar number and intensity of anterior and posterior segment surgical procedures. Our histopathologic findings suggest that the striate keratopathy in those eyes may be caused by endothelial malnutrition resulting from impaired aqueous production secondary to ciliary body dysfunction, rather than from previous surgical trauma. Ample evidence for this hypothesis was present in the enucleated eyes with anterior proliferative vitreoretinopathy and hypotony. In these eyes,

multifocal areas of tractional tearing and tears of the pars plicata ciliary epithelium with denudation of the ciliary processes were uniformly present. These structural findings would be expected to result in both breakdown of the ciliary blood-aqueous barrier at the pars plicata[38] and impaired aqueous secretion. Clinicopathologic findings that suggest breakdown of the ciliary blood-aqueous barrier at the pars plicata in the vitrectomy patients with anterior proliferative vitreoretinopathy, hypotony, and striate keratopathy included ultrastructural presence of fibrin in 30% of the surgically excised membranes and the persistence of aqueous flare in all of the eyes with chronic postoperative hypotony, despite successful retinal reattachment and the absence of rubeosis iridis. The clinical findings of striate keratopathy, hypotony, aqueous flare, and cataract in these eyes are similar to the findings seen in the syndrome of ciliary dysfunction secondary to anterior segment ischemia.[39-42] However, in eyes with anterior proliferative vitreoretinopathy, the clinical findings appear to be manifestations of ciliary dysfunction caused by tractional structural damage to pars plicata ciliary epithelium rather than to ischemia. Neither evidence of ischemic necrosis of the iris or ciliary body nor findings of choroidal vascular congestion or stasis were present in any eye examined clinically or pathologically in our study.

The preoperative clinical finding of the presence of a circumferential ring of opaque, white, fibrous membranes that extended to the pars plicata or iris appeared uniformly predictive of chronic intractable postoperative hypotony. Clinically, this was manifest by the iris findings of a fixed dilated pupil, posterior iris retraction, or entropion uveae. These iris findings were not predictive of chronic postoperative hypotony, however, because eyes with similar adhesions to the iris of either vitreous or more diaphanous anterior proliferative vitreoretinopathy membranes (through which the ciliary processes were visible) uniformly recovered a normal ocular tension after surgical dissection. In the eyes with diaphanous anterior proliferative vitreoretinopathy, preoperative low ocular tension or hypotony appeared principally to be caused by increased aqueous outflow through open, fixed retinal breaks, ciliary breaks, or both, occurring either within or posterior to the posterior margin of the anterior proliferative vitreoretinopathy. Although functional damage to aqueous secretion by the ciliary processes in these eyes appeared minimal, the presence of chronic postoperative aqueous flare in some of these eyes, despite retinal reattachment and the absence of rubeosis irides, suggested that structural damage to the ciliary epithelium had occurred similar to the traction stage in the enucleated eyes. The presence of a circumferential ring of anteriorly adherent, opaque, white, fibrous membranes probably correlated with the more severe stages of anterior proliferative vitreoretinopathy (incorporation and proliferation) and obscured severe tractional damage to the ciliary epithelium of the pars plicata. Intraoperative bleeding from fine vessels within the anterior proliferative vitreoretinopathy membranes in some of the eyes with persistent postoperative hypotony suggested that fibrovascular ingrowth (neovascularization) from the uvea, retina, or both, similar to that seen in the proliferation stage in the enucleated eyes, had occurred. The recovery of a normal postoperative ocular tension in some of the eyes with preoperative hypotony and intermediate opacification of their circumferential ring of anterior proliferative vitreoretinopathy suggested that a lesser degree of tractional damage to the pars plicata was present.

Tractional structural damage to the ciliary epithelium by advanced anterior proliferative vitreoretinopathy may not only result in impaired aqueous secretion and chronic hypotony in some eyes, but may also result in breakdown of the ciliary blood-aqueous barrier and the occurrence of postvitrectomy fibrin syndrome in some eyes.[18] Breakdown of the ciliary blood-aqueous barrier is suggested by the finding of postvitrectomy fibrin deposition only within the surgically excised anterior proliferative vitreoretinopathy membranes but not in coexistent posterior proliferative vitreoretinopathy membranes. In such predisposed eyes, surgical trauma during vitreous base dissection may result in exudation of serum components from the denuded ciliary processes and triggering of the coagulation cascade.[43] In a study of clinical risk factors for postvitrectomy fibrin formation, Jaffe and associates[18] identified aqueous flare as a significant preoperative risk factor and anterior epiretinal membrane dissection as the only intraoperative risk factor associated with the postvitrectomy fibrin syndrome.

According to our proposed mechanism, the severity of postvitrectomy fibrin syndrome would be predicated on the degree of tractional or surgically induced breakdown of the ciliary blood-aqueous barrier. Increasingly severe postvitrectomy fibrin formation would be pre-

dicted to occur in the following: (1) in eyes with a more advanced stage of anterior proliferative vitreoretinopathy (traction, incorporation, proliferation) that clinically are identified by a narrow peripheral trough of forwardly displaced vitreous base, opaque white fibrous membranes with or without visible fibrovascular ingrowth into the membranes; (2) in eyes with a greater number of prior surgical procedures involving the vitreous base, peripheral retina, or ciliary body; (3) in eyes with anterior proliferative vitreoretinopathy requiring extensive surgical manipulation such as vitreous base dissection[43]; and (4) in eyes with marked traction on a vitreous base that was partly adherent to the pars plicata.

The greater quantitative importance of breakdown of the ciliary blood-aqueous barrier as compared to disruption of the blood-retinal barrier in the generation of postvitrectomy fibrin syndrome in these eyes may be partially related to two factors. First, blood flow to the ciliary body is several times greater than retinal blood flow.[44] Disruption of the ciliary blood-aqueous barrier would therefore be expected to produce a more massive outpouring of serum and other fibrin precursors than would a similar disruption of the blood-retinal barrier. Second, the direct tractional effects of the anterior proliferative vitreoretinopathy membranes, as described in our study and of current vitreous base dissection techniques, are more likely to create extensive disruption of the ciliary blood-aqueous barrier than are the direct tractional and epiretinal dissection effects of posterior proliferative vitreoretinopathy.

An important factor in the early pathogenesis of anterior proliferative vitreoretinopathy with associated fibrocellular proliferation is adherence to the pars plicata of more anterior structures. This adhesion may be caused or enhanced by fibrin adherent to lens zonular attachments or other anterior structures. The early formation of this adhesion could be studied ultrastructurally in the ten eyes that underwent vitrectomy with biopsy of their anterior proliferative vitreoretinopathy membranes. In three of the ten eyes, fibrin deposition was detected between the fibrocellular stroma of the anterior proliferative vitreoretinopathy and sheets of ciliary epithelium or iris fragments. Fibrin, presumed to be derived from breakdown of the ciliary blood-aqueous barrier in these eyes, appeared to form a biologic adhesion between the anteriorly displaced vitreous base with its associated fibrocellular proliferation and the nonpigmented ciliary epithelium. The adhesive properties of fibrin have been demonstrated in previous studies[45,46] and has been clinically used in a variety of ophthalmic surgical procedures.[47-49] Adhesion of the anteriorly displaced vitreous base with its associated fibrocellular proliferation to the ciliary processes may cause tractional tearing of the ciliary epithelium of the pars plicata during contraction. This tearing may have resulted in chronic intractable hypotony, repeated cycles of postvitrectomy fibrin formation, and eventual atrophia or phthisis bulbi. The identification of fibrin as a possible biologic adhesive in anterior proliferative vitreoretinopathy in at least some eyes may allow for the successful intraoperative or perioperative use of pharmacologic antifibrin agents, such as heparin[50] or recombinant tissue plasminogen activator,[51,52] to prevent these end-stage sequelae.

Similarly, original lens zonular attachments to the ciliary epithelium of the pars plicata[53] may enhance or provide a firm structural adhesion between the vitreous base and the ciliary epithelium of the pars plicata. Complete removal of the peripheral lens capsule and associated zonular remnants at the time of pars plana lensectomy and vitrectomy, such as with the use of alpha chymotrypsin,[54] may help prevent the occurrence of the severe stages of anterior proliferative vitreoretinopathy associated with intractable hypotony. Meticulous trimming of the anteroperipheral vitreous with scleral indentation, especially in aphakic or pseudophakic eyes, may similarly reduce the likelihood that an anteriorly displaced vitreous base (for example, after scleral buckling or intraocular gas tamponade) will be able to adhere to the pars plicata and result in chronic intractable hypotony.

The mechanism of forward displacement of the vitreous base is important because it may allow contact and adhesion of the vitreous or fibrocellular membranes to the pars plicata, thus setting the stage for subsequent tractional tearing of the epithelium of the ciliary processes. The result is chronic intractable hypotony and an increased risk of severe postvitrectomy fibrin formation. All of the eyes examined in this study, both clinically and pathologically, were either aphakic or pseudophakic. Removal of the lens in these eyes, or violation of the lens-zonular diaphragm during cataract extraction with vitreous loss, may have removed or

disturbed an important mechanical barrier both to marked forward displacement of the vitreous base and to contact and adhesion of the vitreous base to the ciliary processes or more anterior ocular structures. Although other factors[12,55] may also promote marked forward displacement of the vitreous base, fibrocellular contraction of the anteriorly adherent vitreous base appeared to be predominant in the enucleated eyes. Fibrovascular ingrowth from the sclerotomy sites after pars plana vitrectomy was not detected in any eye. Additionally, only two of the ten enucleated eyes with anterior proliferative vitreoretinopathy had a history of previous vitrectomy. Five of the ten enucleated eyes had been treated by scleral buckling procedures alone. In three of the enucleated eyes, no retinal surgical intervention had been performed. The anterior proliferative vitreoretinopathy with hypotony in these three eyes occurred as a primary event in the evolution of the aphakic rhegmatogenous retinal detachment. In three eyes without prior retinal surgery, the finding of severe anterior proliferative vitreoretinopathy with hypotony suggests that anterior proliferative vitreoretinopathy with hypotony may occur primarily as an extension of the wound-healing response to rhegmatogenous retinal detachment and is not merely a complication of current retinal detachment surgical techniques.

Our clinicopathologic findings suggest that proliferative vitreoretinopathy is an extension of the physiologic wound-healing response to rhegmatogenous retinal detachment. Posterior proliferative vitreoretinopathy is generally an avascular process that is characterized by retinal pigment epithelium, glial, and fibrocyte proliferation in association with an extracellular matrix of original vitreous collagen and internal limiting membrane. Anterior proliferative vitreoretinopathy initially occurs as an extension of posterior proliferative vitreoretinopathy with contraction of the residual vitreous base. Anterior proliferative vitreoretinopathy appears to evolve, however, in three consecutive stages: traction, incorporation, and proliferation. Progressive structural damage to the ciliary body by contraction of the anterior proliferative vitreoretinopathy may result in permanent impairment of aqueous secretion and chronic intractable hypotony. Breakdown of the blood-aqueous barrier from traction on the ciliary epithelium or in advanced stages, from neovascularization of the vitreous base, adds a vascular component to this wound-healing response and may be associated with clinically significant fibrin formation.

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OPHTHALMIC MINIATURE

The reference was clearly to a nonhuman species . . . Their disguise, however, became transparent in the face of the following observations by the author. It was at once obvious the author knew everything. Knew everything—and was taking it in his stride. The line (and I tremble remembering it even now) read:

. . . his eyes slowly roved about the room.

Vague chills assailed me. I tried to picture the eyes. Did they roll like dimes? The passage indicated not; they seemed to move through the air, not over the surface. Rather rapidly, apparently. No one in the story was surprised. That's what tipped me off. No sign of amazement at such an outrageous thing. Later the matter was amplified.

. . . his eyes moved from person to person.

There it was in a nutshell. The eyes had clearly come apart from the rest of him and were on their own. My heart pounded and my breath choked in my windpipe. I had stumbled on an accidental mention of a totally unfamiliar race. Obviously non-Terrestrial. Yet, to the characters in the book, it was perfectly natural—which suggested they belonged to the same species.

And the author? . . . Evidently, he felt this was quite a usual thing. He made absolutely no attempt to conceal this knowledge. The story continued:

. . . presently his eyes fastened on Julia.

Julia, being a lady, had at least the breeding to feel indignant. She is described as blushing and knitting her brows angrily. At this, I sighed with relief. They weren't *all* non-Terrestrials. The narrative continues:

. . . slowly, calmly, his eyes examined every inch of her.

Great Scott! But here the girl turned and stomped off and the matter ended. I lay back in my chair gasping with horror.

Philip K. Dick, *The Collected Stories of Philip K. Dick*, vol. 3., "The Eyes Have It"
New York, Carol Publishing Group, 1987, p. 27–28

Short-term Effects of Levobunolol on Ocular Pulsatile Flow

Marc E. Bosem, M.D., Moshe Lusky, M.D., and Robert N. Weinreb, M.D.

In a randomized, double-masked, placebo-controlled study, we evaluated the effect of levobunolol 0.5%, a nonselective beta-blocker, on intraocular pressure, volume amplitude, and ocular pulsatile flow in healthy individuals and patients with glaucoma. Volume amplitude and ocular pulsatile flow were derived from measurements of pulse amplitude with a pneumatonometer. Two hours after instillation of levobunolol, intraocular pressure decreased from 26.0 ± 5.1 mm Hg to 17.8 ± 3.9 mm Hg (28.3%) ($P < .001$) in glaucomatous eyes and 20.2 ± 3.6 mm Hg to 14.5 ± 4.2 mm Hg (29.6%) ($P < .001$) in healthy eyes. Ocular pulsatile flow was increased after treatment with levobunolol from 482.1 ± 133.3 μl/minute to 548.5 ± 180.3 μl/minute (13.3%) ($P < .006$) in glaucomatous eyes and 457.6 ± 178.2 μl/minute to 528 ± 223.8 μl/minute (12.3%) ($P > .05$) in healthy eyes. There was no significant change in intraocular pressure, volume amplitude, or ocular pulsatile flow in placebo-treated eyes. The implication of these data for glaucoma therapy is not clear. Although we used an instrument that supposedly measures total pulsatile flow, it may be that optic nerve blood flow is dependent on total, both pulsatile and nonpulsatile, flow. Further, even though retinal blood flow is a small component of total ocular blood flow, it may be equally or more important than choroidal flow because of the necessity to maintain the perfusion of the retinal ganglion cells.

THE MECHANISMS of optic nerve damage in glaucoma have not been elucidated clearly. Although both high intraocular pressure and optic nerve ischemia at the level of the lamina cribrosa have been proposed as contributing factors, current therapy for glaucoma is directed only at the former and consists of lowering intraocular pressure. Reducing intraocular pressure by medical or surgical means has been shown to prevent or delay visual field loss in many patients with ocular hypertension[1,2] or primary open-angle glaucoma.[3]

For more than ten years, topically administered beta-adrenergic blocking agents have been the most widely used initial treatment to lower intraocular pressure. In general, they are effective hypotensive agents with few ocular and systemic side effects when administered properly. However, the influence of these drugs on optic nerve blood flow is not clear.

The blood supply to the optic nerve head at the level of the lamina cribrosa is provided mainly by the short posterior ciliary arteries, branches from the peripapillary choroidal arteries, and choroidal arterioles.[4] Hence, impaired choroidal blood flow could result in ischemia with consequent glaucomatous damage to the optic nerve. Because choroidal blood flow is the major component of ocular blood flow,[5] it has been suggested that one method for reasonably approximating choroidal blood flow is to measure ocular pulsatile flow.[6]

In this study, we assessed the short-term effect of the nonselective beta-adrenergic blocking agent, levobunolol, on ocular pulsatile flow in healthy subjects and patients with glaucoma.

Subjects and Methods

Fourteen healthy individuals and 14 patients with primary open-angle glaucoma were enrolled in the study. Informed consent was obtained from all participants. Patients with primary open-angle glaucoma had intraocular pressure of greater than 21 mm Hg on two or

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From the Department of Ophthalmology, University of California, San Diego. This study was supported in part by a grant from Allergan Pharmaceuticals, Irvine, California.

Reprint requests to Robert N. Weinreb, M.D., UCSD/Shiley Eye Center-0946, 9500 Gilman Dr., La Jolla, CA 92093-0946.

more occasions, characteristic visual field defects, glaucomatous optic neuropathy, and refractive error of less than 5 diopters. Healthy control subjects had intraocular pressure less than 21 mm Hg on two or more occasions, normal-appearing optic nerves, refractive error of less than 5 diopters, and no family history of glaucoma. Patients were excluded from the study if they were diabetic or taking oral vasoactive medications. Patients with glaucoma either were never treated with ocular hypotensive medications or had topical medications discontinued at least two weeks before the study. Each group included nine women and five men. The mean age of healthy subjects was 52.0 years (range, 36 to 74 years). Mean age of the patients with glaucoma was 63.9 years (range, 40 to 77 years). These data are shown in Tables 1 and 2.

After the instillation of one drop of topical anesthetic (0.5% proparacaine) in each eye, Goldmann applanation tonometry was performed on each subject in the sitting position. Each subject was then placed supine for two minutes. Baseline heart rate (brachial pulse), blood pressure, and ocular pulse measurements were recorded. All measurements were obtained between 8 and 10 A.M. After baseline measurements, one drop (35 μl) of levobunolol 0.5% (Allergan Pharmaceuticals, Irvine, California), a nonselective beta-adrenergic blocking agent, was instilled in one eye; the fellow eye received a drop of an artificial tear (Refresh, Allergan America, San Juan, Puerto Rico) as a control. The eye treated with levobunolol was selected randomly. The nasolacrimal ducts were occluded for two minutes by the investigator administering the eyedrops in order to diminish their systemic absorption. Two hours after drug instillation, heart rate, blood pressure, volume amplitude, ocular pulsatile flow, and intraocular pressure measurements were obtained again. Mean blood pressure was calculated as the sum of the diastolic pressure plus one third of the difference between the systolic and diastolic blood pressures.

To measure volume amplitude and ocular pulsatile flow we used an ocular pulsatile flow system (Ocular Blood Flow Laboratories, Annapolis, Maryland). This device consists of a pneumatonometer to record pressure pulsations and a personal computer programmed to convert the ocular pulse measurements to ocular volumes and thereby calculate the pulsatile component of total ocular blood flow. Four five-second ocular pulse measurements were analyzed for each eye. To diminish interobserv-

TABLE 1
OCULAR PULSATILE FLOW AND INTRAOCULAR PRESSURE IN 14 PATIENTS WITH PRIMARY OPEN-ANGLE GLAUCOMA

PATIENT NO., AGE (YRS), GENDER	INTRAOCULAR PRESSURE (GOLDMANN)* (MM HG)			OCULAR PULSATILE FLOW* (μL/MIN)		
	BASELINE	2 HRS	% CHANGE	BASELINE	2 HRS	% CHANGE
1, 61, F	35	28	−20	548	696	+27
2, 77, F	26	16	−38	531	629	+18
3, 67, F	24	17	−28	397	437	+10
4, 66, M	34	21	−38	313	296	−5
5, 68, F	28	16	−28	517	642	+24
6, 66, M	22	22	0	277	352	+27
7, 74, F	25	13	−47	797	927	+16
8, 72, F	22	15	−31	400	435	+8
9, 54, F	22	15	−31	604	726	+20
10, 46, M	32	15	−53	598	568	−5
11, 40, F	17	17	0	483	499	+3
12, 74, M	28	20	−29	388	470	+21
13, 66, M	25	19	−24	469	385	−18
14, 64, F	20	14	−30	447	617	+29
63.9	26.0	17.8	−28.3	482.1	548.5	+13.3
(10.7)†	(5.1)	(3.9)		(133.3)	(180.3)	

*Measurement at baseline (between 8 and 10 A.M.) and two hours later.
†Values represent mean (standard deviation).

TABLE 2
OCULAR PULSATILE FLOW AND INTRAOCULAR PRESSURE IN 14 HEALTHY INDIVIDUALS

SUBJECT NO., AGE (YRS), GENDER	INTRAOCULAR PRESSURE (GOLDMANN)* (MM HG)			OCULAR PULSATILE FLOW* (μL/MIN)		
	BASELINE	2 HRS	% CHANGE	BASELINE	2 HRS	% CHANGE
1, 68, F	20	14	−28	836	821	−2
2, 62, F	19	14	−26	365	376	+3
3, 37, M	18	12	−34	328	365	+11
4, 36, M	19	17	−11	313	297	−5
5, 42, F	20	14	−30	759	1011	+33
6, 55, F	22	17	−24	561	672	+19
7, 42, F	22	16	−27	336	412	+22
8, 71, M	22	18	−17	375	400	+7
9, 67, M	17	8	−50	324	†	†
10, 74, F	15	6	−60	290	†	†
11, 56, F	24	19	−21	291	476	+64
12, 42, M	19	16	−16	577	383	−34
13, 37, F	17	10	−41	537	†	†
14, 45, F	26	20	−30	515	597	+16
52.0	20.2	14.5	−29.6	457.6	528.1	+12.3
(13.8)‡	(3.6)	(4.2)		(178.2)	(223.8)	

*Measurement at baseline (between 8 and 10 AM) and two hours later.
†Pulsatile flow measurement was unobtainable because of low intraocular pressure.
‡Values represent mean (standard deviation).

er bias, all pulse measurements were recorded by the same person, who was masked to the treated eye. Hence, the study was double-masked. The pneumatonometer calibration was checked against a Silastic membrane at a pressure of both 15 and 40 mm Hg before each measurement. The pneumatonometer was interfaced with a personal computer programmed with algorithms that calculated average pulse amplitude, ocular volume, and pulsatile ocular blood flow for each of the five-second ocular pulse recordings, by using the method of Langham and associates.[6] Using the intraocular pressure measurements for each pulse, we also calculated the ocular volume with the equation derived by Grajewski and associates.[7] The ocular volume amplitude was derived from the difference between maximum and minimum volume (Table 3). To assess reproducibility of ocular pulsatile flow, we calculated coefficient of variation (standard deviation/mean) of three replicated measurements on 27 subjects (15 with glaucoma and 12 healthy). The average coefficient of variation was 7.1% (7.5% and 6.7% for subjects with glaucoma and healthy subjects, respectively); this did not correlate with the magnitude of ocular pulsatile flow.

Ocular pulsatile flow, ocular pulsatile volume, and intraocular pressure data were compared with a paired *t*-test. A probability of .05 was considered significant.

Results

Two hours after levobunolol administration, intraocular pressure in the treated glaucomatous eyes decreased by 8.2 mm Hg (28.3%) ($P < .001$), and for treated normal eyes decreased by 5.7 mm Hg (29.6%) ($P < .001$). There was no significant change in intraocular pressure in contralateral eyes. Tables 1 and 2 show intraocular pressure measurements before and two hours after levobunolol administration in patients with glaucoma and healthy subjects, respectively.

Table 3 shows the ocular volume amplitude measurements before and two hours after levobunolol administration. Volume amplitude did not change significantly after treatment in glaucomatous eyes. In healthy subjects, ocular pulse volume significantly increased ($P < .05$) two hours after levobunolol administration. Contralateral eyes in both groups were unchanged.

TABLE 3
OCULAR VOLUME AMPLITUDE IN HEALTHY EYES AND EYES WITH PRIMARY OPEN-ANGLE GLAUCOMA*

GLAUCOMATOUS EYES			HEALTHY EYES		
BASELINE	2 HRS	% CHANGE	BASELINE	2 HRS	% CHANGE
7.3	6.9	−6	10.3	8.6	−16
4.8	5.5	15	4.2	3.5	−18
4.2	4.3	39	2.4	4.2	71
4.1	3.5	−15	3.9	5.5	41
4.8	4.0	−15	6.9	9.9	42
3.1	2.7	−16	6.0	7.9	32
7.4	7.7	33	2.9	3.0	4
4.0	4.5	15	3.9	5.0	31
8.0	8.3	4	3.4	8.7	157
5.6	4.9	−13	3.0	9.4	210
4.6	4.9	7	3.9	4.7	20
5.4	7.0	30	6.8	5.3	−22
3.6	4.0	13	5.7	7.7	36
5.5	6.6	20	5.7	6.3	12
5.2 (1.5)†	5.3 (1.7)	3	4.9 (2.1)	6.4 (2.3)	42

*Ocular volume amplitude (μl).
†Values represent mean (standard deviation).

Tables 1 and 2 show the ocular pulsatile flow measurements before and two hours after levobunolol administration. In the patients with glaucoma, pulsatileflow was significantly increased in treated eyes ($P < .006$). Although pulsatile ocular flow also increased in the healthy individuals, this change was not statistically significant. Three of the eyes in the healthy controls had treated intraocular pressure that was lower than 10 mm Hg. At such low pressure, pulsatile flow could not be measured. In both groups, pulsatile flow in contralateral eyes was unchanged.

In the glaucoma group, heart rate was 71 ± 8.5/minute baseline and 69 ± 7.4/minute after two hours, and mean blood pressure was 94 ± 11.5 mm Hg baseline and 95 ± 10.2 mm Hg after two hours. In the healthy group, heart rate was 66 ± 6.8/minute baseline and 65 ± 5.9/minute after two hours, and mean blood pressure was 87 ± 8.2 mm Hg baseline and 88 ± 8.7 mm Hg after two hours. There was no significant change in heart rate or mean blood pressure in either group.

Discussion

After administration of levobunolol, a nonselective beta-adrenergic blocking agent, we observed ocular pulsatile flow to be significantly increased in eyes with primary open-angle glaucoma. Pulsatile flow also was increased in normal eyes. However, there was not sufficient power to detect a 12.3% increase as significant with a sample size of 14 patients in whom pulsatile flow could be appropriately evaluated in only 11. The implication of these data for glaucoma therapy is not clear, because it is not precisely known what physiologic factor was actually assessed with the employed methods.

Several techniques of measuring blood flow noninvasively in human eyes have been proposed. These include methods for assessment of total ocular blood flow (ophthalmodynamometry), assessment of microcirculation of the optic nerve head (fluorescein angiography), and measuring retinal and choroidal blood flow (indocyanine green fundus angiography). The instrument used in our study supposedly measures total ocular pulsatile flow. Using a pneumatonometer, the ocular pulse is recorded. A pressure-volume relationship for the human eye, as developed from data provided by Eisenlohr, Langham, and Maumenee,[8] is used then to derive ocular volume from intraocular pressure. Finally, pulsatile ocular blood flow, which has been suggested to account for the major portion of blood flow to the eye,[6] is determined by calculating the change in ocular volume over time.

In order to determine ocular pulsatile flow with this instrument, several assumptions are made. First, it is assumed that the majority of ocular flow is choroidal. Alm and Bill[9] measured blood flow in the monkey eye and found that the choroid accounted for over 90% of total flow. Second, it is assumed that the ocular blood flow is principally pulsatile. Michelson and colleagues[10] used an ultrasound Doppler probe to measure blood velocity of the ophthalmic artery and found that diastolic blood velocity was minimal. It is not known, however, how blood velocity relates to flow, and specifically whether diastolic blood velocity corresponds to nonpulsatile flow. Because the instrument we used measures only pulsatile flow, it is not possible to recognize changes in the nonpulsatile component. Third, it is assumed that the pressure-volume relationship used by the instrument to calculate ocular volume is valid for all eyes. However, this relationship was developed from data on only three enucleated eyes and six living eyes.[8] It is not known how differences in scleral rigidity, eye volume, and axial length affect the derived relationship and, hence, the calculation of ocular volume and flow. In individuals with severe myopia, who are known to have a low scleral rigidity and high axial length, the accuracy of this technique has been questioned.[11] Further, the effect of ocular hypotensive drugs on scleral rigidity is also not known.

Our data showing an increase in ocular perfusion in healthy subjects and patients with glaucoma contrast with those previously reported with timolol, another nonselective beta-adrenergic blocking agent. In those previous studies, timolol was reported to decrease ocular pulsatile flow in healthy subjects and patients with glaucoma.[12] In a short-term study with healthy eyes that used the same technique as our study, Yoshida and colleagues[13] reported a significant decrease in ocular volume amplitude and ocular pulsatile flow two hours after one drop of timolol 0.5%. Likewise, but in a long-term study, Langham[12] found pulsatile ocular blood flow was decreased after daily treatment of glaucomatous eyes with timolol for one year. Several factors may account for the discrepancies between the current study and previous reported studies, including the possible systemic absorption of drug through the nasolacrimal duct, differences in pharmacokinetics between the two drugs, differences in pulsatile/nonpulsatile blood flow after drug administration, or duration of drug administration.

With systemic absorption of a topical beta-adrenergic blocking agent, heart rate is lowered,[14] which may result in a lower ocular pulsatile flow (calculated from volume change/time interval per pulse). Although the design of our study was similar to that of Yoshida and colleagues,[13] they did not note whether nasolacrimal duct occlusion was used. A decrease in heart rate was observed in their study, which may explain the decrease in volume amplitude and pulsatile flow, and suggests the systemic absorption of the timolol. However, if nasolacrimal duct occlusion accounts for the difference in ocular pulsatile flow data, we speculate that nasolacrimal duct occlusion or another similar technique such as eyelid closure may be important for optimal ocular pulsatile flow after drug administration.

Another possible explanation for differences between our data and those of Yoshida and colleagues[13] is that the two beta-blockers studied, timolol and levobunolol, do not have the same pharmacokinetics. Both drugs are nonselective beta-adrenergic blocking agents with comparable ocular hypotensive actions; however, their rates of uptake and diffusion may not be the same. It is known that topically applied drugs diffuse through the cornea into the anterior chamber and then some component continues to diffuse posteriorly to the retina and choroid.[15] Inasmuch as several reports have demonstrated the presence of beta-2 receptors in the choroidal vasculature,[7,16,17] and as beta blockade results in vasoconstriction,[18] drug diffusion into the choroid may cause vasoconstriction. If uptake and diffusion of the drugs are different, then comparable amounts would have different effects. When compared to timolol, levobunolol has a greater corneal permeability and lipophilicity, which combined should result in higher drug uptake into the aqueous after a single topical administration.[19] However, once absorbed into the aqueous, levobunolol is transformed to an active, more polar metabolite, dihydrolevobunolol.[20] The polarity of this active metabolite may inhibit its diffusion into the retina and choroid with less subsequent vasoconstriction. In this case, ocular pulsatile flow would be higher.

Finally, because the instrument we used to measure ocular pulsatile flow only measures the pulsatile component, changes in nonpulsatile flow, which occur during diastole, are not assessed. With vasoconstriction, local diastolic blood pressure should increase, which could change the proportion of nonpulsatile flow rel-

ative to the total. Should nonpulsatile flow increase relative to pulsatile flow, then total flow to the eye would be greatly underestimated by merely measuring pulsatile flow. Therefore, greater nonpulsatile flow might compensate for the decreases in pulsatile flow reported by Yoshida and colleagues.[13]

In contrast to previous studies that found volume amplitude to be decreased after timolol administration,[12,13] we found ocular volume amplitude to be either increased, in levobunolol-treated healthy eyes, or unchanged, in treated glaucomatous eyes. The lower ocular volume amplitude after timolol treatment may be indicative of choroidal vasoconstriction. Grajewski and colleagues[7] noted that because most of the change in ocular volume during each pulse occurs in the choroid, and is dependent upon the elastic properties of the vessels, increased choroidal vascular tone may result in decreased volume amplitude per pulse. If there are no changes in heart rate and blood pressure, lower ocular pulse amplitude is indicative of choroidal vasoconstriction and may result in an increase in the ratio of nonpulsatile to pulsatile flow. After a single administration of topical timolol, ocular volume amplitude was reported as either unchanged[7] or decreased[18] in healthy eyes. Without systemic hemodynamic changes, an increased or unchanged volume amplitude, as we observed, would indicate the lack of significant vasoconstriction in the choroid.

Our observations are based on measuring pulsatile flow after only a single administration of levobunolol. After several doses, both levobunolol and timolol are stored in ocular tissues[21] in high enough concentrations to allow for once-daily use in many patients. However, these higher concentrations of drug may result in increased diffusion, choroidal vasoconstriction, and, therefore, decreased volume amplitude and pulsatile flow. Langham[12] observed such a decrease in pulsatile flow after long-term administration of timolol in six patients with primary open-angle glaucoma.

The significance of our study to the pharmacologic treatment of glaucoma remains to be determined. Although we used an instrument that supposedly measures total pulsatile flow, it may be that optic nerve blood flow is dependent on total, both pulsatile and nonpulsatile, flow. Further, even though retinal blood flow is a small component of total ocular blood flow, it may be equally or more important than choroidal flow because of the necessity to maintain the perfusion of the retinal ganglion cells. If a treatment for glaucoma lowers intraocular pressure, but concomitantly reduces necessary blood flow, then the risk of optic nerve fiber ischemia may have more impact than the benefits of ocular hypotension. Conversely, there may be advantages to treatments that lower intraocular pressure and simultaneously increase pulsatile or retinal blood flow.

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OPHTHALMIC MINIATURE

Though Jason's eyelids were lowered in their deep sockets, and seemed to shudder in the firelight, Carol's blue eyes were alertly round and her face as pristine and blank as a china statuette's each time the slow music turned her around so Ed could see her.

John Updike, *Trust Me*, "The Other Woman"
New York, Alfred A. Knopf, 1987, p. 281

Macular Phototoxicity Caused by Fiberoptic Endoillumination During Pars Plana Vitrectomy

Mark Michels, M.D., Hilel Lewis, M.D., Gary W. Abrams, M.D., Dennis P. Han, M.D., William F. Mieler, M.D., and Jay Neitz, Ph.D.

Three cases of retinal phototoxicity were caused by light from the endoilluminator used in vitrectomy. Preoperative clinical examination, color photography, and fluorescein angiography in all three cases failed to disclose retinal pigment epithelial changes. Postoperative clinical findings, photographs, and fluorescein angiograms are highly suggestive of the presence of retinal phototoxicity. The characteristics of these lesions and surgical conditions implicate the endoilluminator as the source of photic injury. The macular lesions were noted within one week of the surgical procedure, measured between 2 and 5 disk diameters in size, involved the fovea in two eyes, and resulted in marked decrease in visual acuity in two of three eyes, with persistence in one eye. Initially, whitening of the outer retina was present, but was replaced by pigmentary mottling at the level of the retinal pigment epithelium within a few weeks. Preventive measures to avoid macular phototoxicity associated with vitrectomy are discussed.

RETINAL PHOTOTOXICITY attributed to the operating microscope has been described after many ophthalmic surgical procedures including vitrectomy,[1] and has been extensively reviewed.[2] The first case attributed to the intraocular light source used in vitrectomy was described after epiretinal membrane dissection and was attributed to prolonged exposure to direct illumination during dissection of particularly adherent epicenters.[3] One additional case of endoilluminator-related retinal phototoxicity has been described in humans and also occurred during dissection of a difficult epiretinal membrane.[4] Mottling of the retinal pigment epithelium has been described after a macular hole surgical procedure and, although not addressed in pre- or postoperative photographs, has been attributed to the light of the endoilluminator.[5] To these cases we add three additional cases of macular phototoxicity caused by the fiberoptic endoilluminator. We studied the shared features of these three cases and preventive measures.

Patients and Methods

During the two-year period between 1989 and 1991, four of us (H.L., G.W.A., D.P.H., and W.F.M.) operated on 132 eyes (132 patients) with epiretinal membranes in the macular region and recognized three eyes (three patients, 2.3%) that developed postoperative macular lesions consistent with retinal phototoxicity. All three patients were examined pre- and postoperatively and were operated on by one of us at the Jules Stein Eye Institute or at the Medical College of Wisconsin. A complete ocular history and examination were performed in each case. Preoperative and postoperative examinations included contact-lens fundus biomicroscopy, indirect ophthalmoscopy, and fluorescein angiography. The surgical procedure included a three-port pars plana vitrectomy and removal of the epiretinal membrane by using a barbed microvitreoretinal blade and intraocular for-

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From the Retina Division, Jules Stein Eye Institute and Department of Ophthalmology, UCLA School of Medicine, Los Angeles, California (Drs. Michels and Lewis); and the Eye Institute, Medical College of Wisconsin, Milwaukee, Wisconsin (Drs. Abrams, Han, Mieler, and Neitz). This study was supported in part by a manpower award from Research to Prevent Blindness, Inc., New York, New York (Dr. Lewis); by the Charles Kenneth Feldman Fund, Los Angeles, California (Dr. Lewis); and by an unrestricted grant from Research to Prevent Blindness, Inc., New York, New York, to the Eye Institute, Medical College of Wisconsin, Milwaukee, Wisconsin.

Reprint requests to Hilel Lewis, M.D., Jules Stein Eye Institute, 100 Stein Plaza, Los Angeles, CA 90024-7007.

ceps. The Grieshaber (Langhorne, Pennsylvania) or Trek (Mukwonago, Wisconsin) light source using maximum illumination was used. The cornea was covered when no intraocular operation was being performed to minimize retinal exposure to the operating microscope light in all cases.

Case Reports

Case 1

A 43-year-old woman was referred to us in December 1991 with a macular pucker in her left eye. Her ocular and medical history were remarkable for bilateral acute retinal necrosis in 1981, and multiple sclerosis in 1986. The right eye developed a retinal detachment and after failed surgical therapy, the eye was enucleated in 1983. The left eye developed neovascularization at the optic nerve head for which panretinal photocoagulation was performed in 1981. Between 1981 and 1986, the patient had transient neurologic symptoms including intermittent decreases in vision that lasted approximately one week, but were unassociated with retrobulbar pain on eye movement. Magnetic resonance imaging demonstrated findings typical of multiple sclerosis, which was thought to account for her symptoms. Since 1986, she complained of intermittent disturbances of vision approximately three to four times per year. With systemic prednisone, which she had taken since 1989, the symptoms resolved.

Until 1989, the visual acuity in the left eye could be corrected to 20/25. Since then, she noted a slowly progressive decrease in visual acuity and metamorphopsia in the left eye. In 1990, she was unable to drive and required low-vision aids to read. Our first examination on Dec. 5, 1990, disclosed a best-corrected visual acuity of 20/125. Anterior segment examination showed no signs of active inflammation and no neovascularization of the iris. The lens and vitreous were clear. The optic nerve head showed mild temporal pallor and was sharp. In the macular region, there was an epiretinal membrane with a pseudohole and mild retinal vascular tortuosity (Fig. 1). Peripheral photocoagulation scars were noted posterior to the area of previous retinal necrosis. Fluorescein angiography demonstrated no retinal pigment epithelial hyperfluorescence or marked macular edema (Fig. 2). After discussing the alternatives with the patient, she decided to undergo pars plana vitrectomy and membrane dissection, which was performed one week later. Intraoperatively, the epiretinal membrane was friable, adhered to the retina, and difficult to remove. The intraocular endoilluminator and light source were used. External illumination was provided by an operating microscope fitted with a 100-W halogen bulb transmitted with a fiberoptic cable. Total surgical time was one hour 50 minutes. Skin temperature varied from 33.8 to 34.5 C. Oxygen saturation was 99%. On the first postoperative day, her visual acuity was hand movements. By indirect ophthalmoscopy and biomicroscopy, a creamy oval area at the level of the deep retina and involving the fovea was noted. This area measured approximately 4 × 5 disk diameters. Photographs taken one week postoperatively demonstrated that this discrete lesion primarily involved the retinal pigment epithelium (Fig. 3). Fluorescein angiography performed two weeks postoperatively demonstrated discrete early mottled hyperfluorescence with late staining in the affected area (Fig. 4, left). Late staining of the overlying retinal vein could also be seen (Fig. 4, right). In March 1991, the visual acuity improved to 20/300 and the macular lesion showed mottled pigmentation. The patient was last examined in October 1991, at which time the visual acuity remained at 20/300.

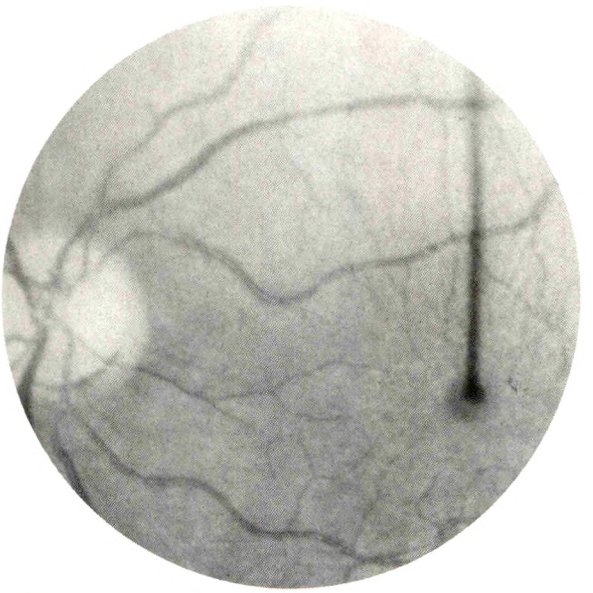


Fig. 1 (Michels and associates). Case 1. Preoperative photograph of the left eye shows an epimacular membrane. Visual acuity was 20/125.

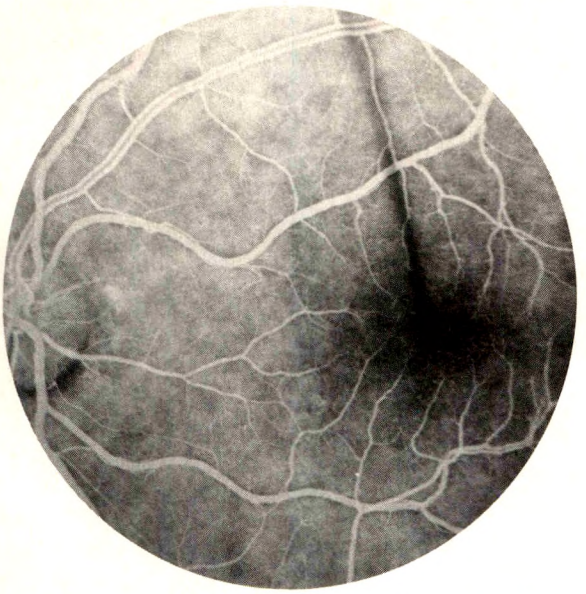


Fig. 2 (Michels and associates). Case 1. Preoperative fluorescein angiogram shows normal retinal and choroidal vascular filling.

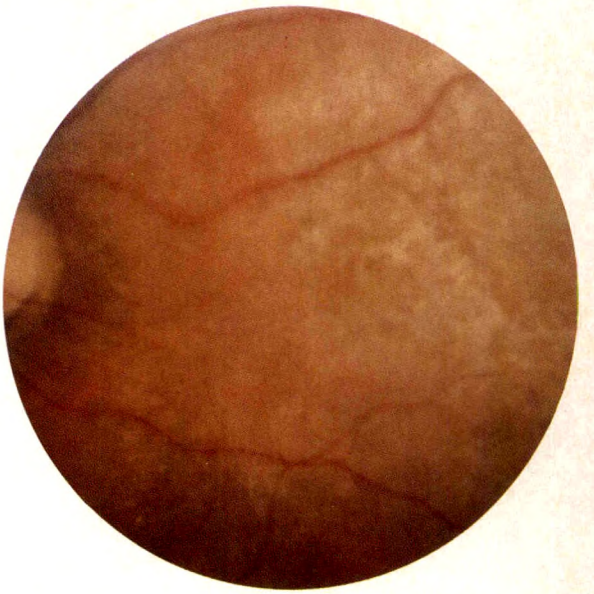


Fig. 3 (Michels and associates). Case 1. One week after vitrectomy, a creamy oval discrete lesion involving the outer retina and retinal pigment epithelium was seen in the macula region. Visual acuity was hand motions.

Case 2

A 76-year-old woman who had a five-month history of blurred vision in her right eye was examined in April 1991. Her best-corrected visual acuity was R.E.: 20/200 and L.E.: 20/20. The anterior segment was normal. Examination of the right eye with biomicroscopy and indirect ophthalmoscopy showed a prominent macular epiretinal membrane causing tractional elevation of the fovea (Fig. 5). There were prominent retinal striae and retinal microvascular abnormalities on the superior edge of the

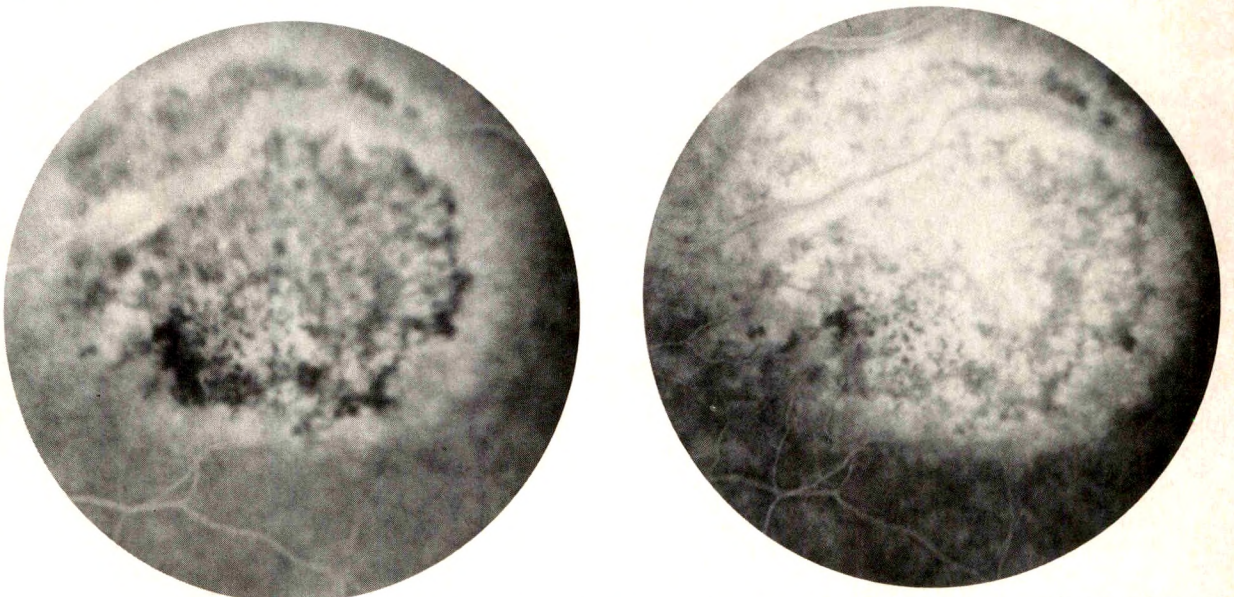


Fig. 4 (Michels and associates). Case 1. Postoperative fluorescein angiogram. Left, Early phase shows a discrete lesion with mottled fluorescence and hyperfluorescent margins. Right, Venous phase shows increased fluorescence and staining of the retinal vein overlying the lesion and at the level of the sclera.

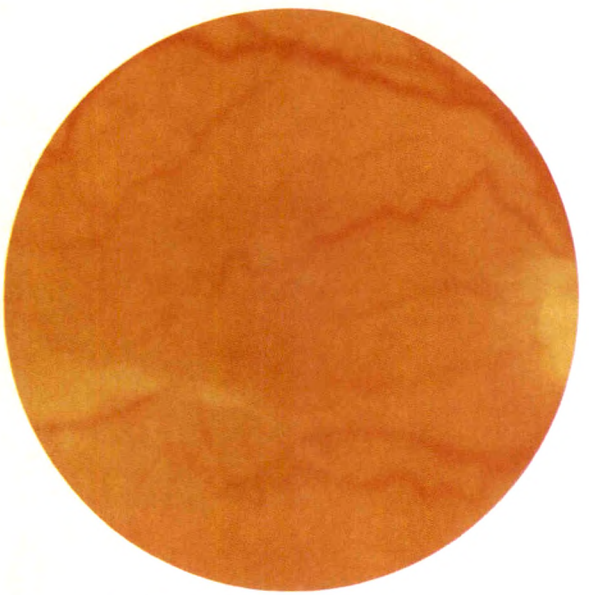


Fig. 5 (Michels and associates). Case 2. Prominent epiretinal membrane causing a tractional detachment of the fovea. Visual acuity was 20/200.

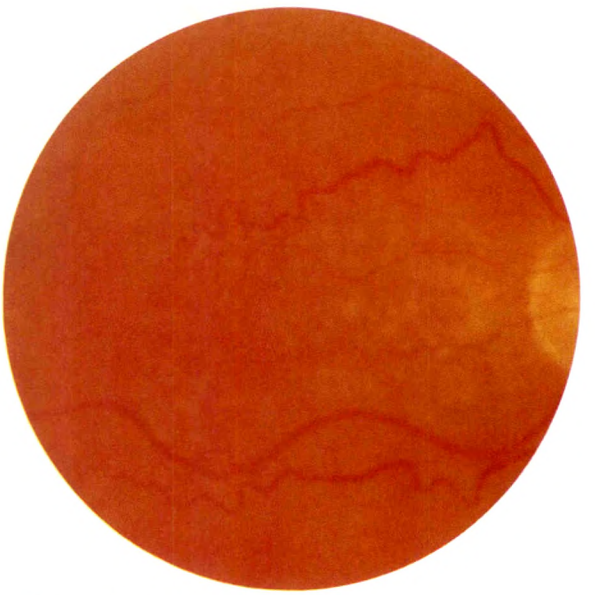


Fig. 6 (Michels and associates). Case 2. Three weeks postoperatively, the right eye demonstrated pigment clumping in the papillomacular bundle and surrounding the fovea. Visual acuity was 20/400.

epiretinal membrane. Pigmentary changes were not present. Fluorescein angiography also failed to show abnormalities at the level of the retinal pigment epithelium. On April 16, 1991, she underwent a three-port pars plana vitrectomy and membrane dissection in the right eye.

A thick and linear epiretinal membrane that extended across the macula was easily removed. Another epiretinal membrane on the inferonasal edge of the macula was also removed. The traction on the macula was released and no complications occurred. At the

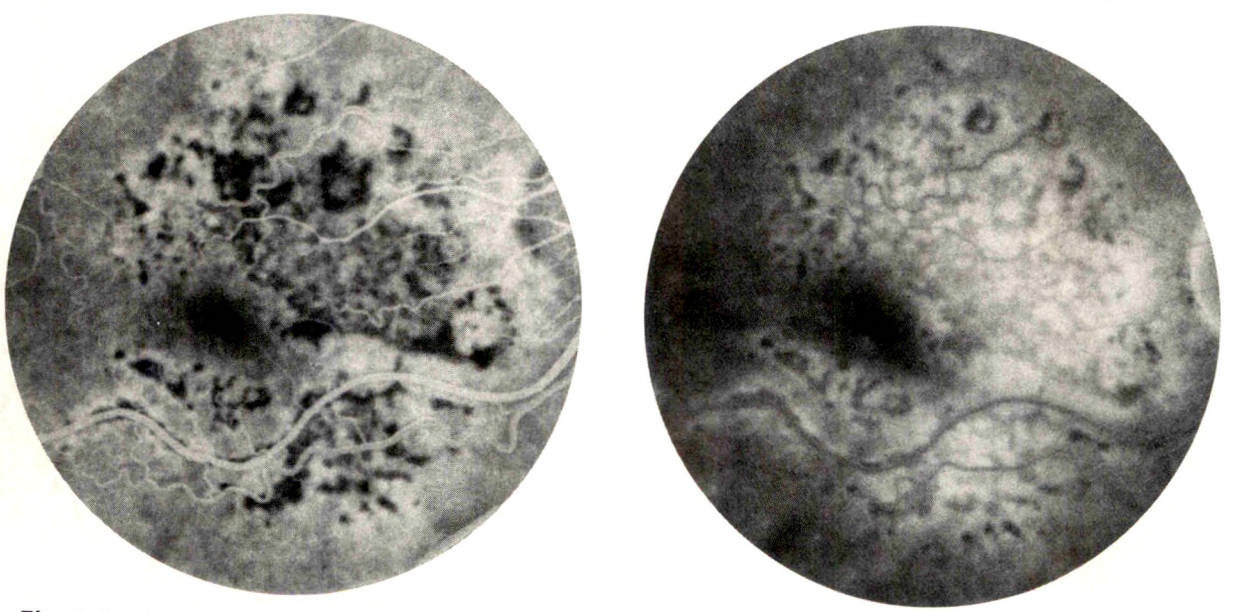


Fig. 7 (Michels and associates). Case 2. Postoperative fluorescein angiogram. Left, Arteriovenous phase demonstrated mottled fluorescence of the lesion surrounding the fovea and in the papillomacular bundle. Right, Late phase of the angiogram shows staining of the area corresponding to the pigmentary disturbance noted clinically.

end of the surgical procedure, cryotherapy was used to treat two preexisting anterior retinal tears, and a fluid-air exchange was performed. Total surgical time was one hour 50 minutes, and the intraocular endoilluminator and light source were used. External illumination was provided by a microscope fitted with a 50-W tungsten filament bulb. The patient's intraoperative core temperature was 35.0 to 35.3 C. The oxygen saturation was 99%.

One week postoperatively, visual acuity in the right eye was 20/400 and retinal examination disclosed macular edema. Three weeks postoperatively, hypopigmented mottling throughout the nasal portion of the macula and surrounding the fovea was noted at the level of the retinal pigment epithelium (Fig. 6). Fluorescein angiography showed early hyperfluorescence and late staining in the area where the pigmentary changes were seen clinically (Fig. 7). Four months postoperatively, the visual acuity in her right eye had improved to 20/60−2, although the macular pigmentary changes remained unchanged.

Case 3

A 72-year-old man with a visual acuity of 1/200 in the right eye underwent a pneumatic retinopexy for a macula-off rhegmatogenous retinal detachment on Aug. 26, 1988. On Sept. 29, 1988, visual acuity had improved to 20/80 and the retina was totally attached. On Dec. 28, 1988, the visual acuity in the right eye decreased to 20/200 because of the development of an epiretinal membrane in the macular region (Fig. 8). On March 3, 1989, a pars plana vitrectomy and epiretinal membrane dissection



Fig. 8 (Michels and associates). Case 3. Four months after pneumatic retinopexy, an epimacular membrane was noted. Visual acuity was 20/200.

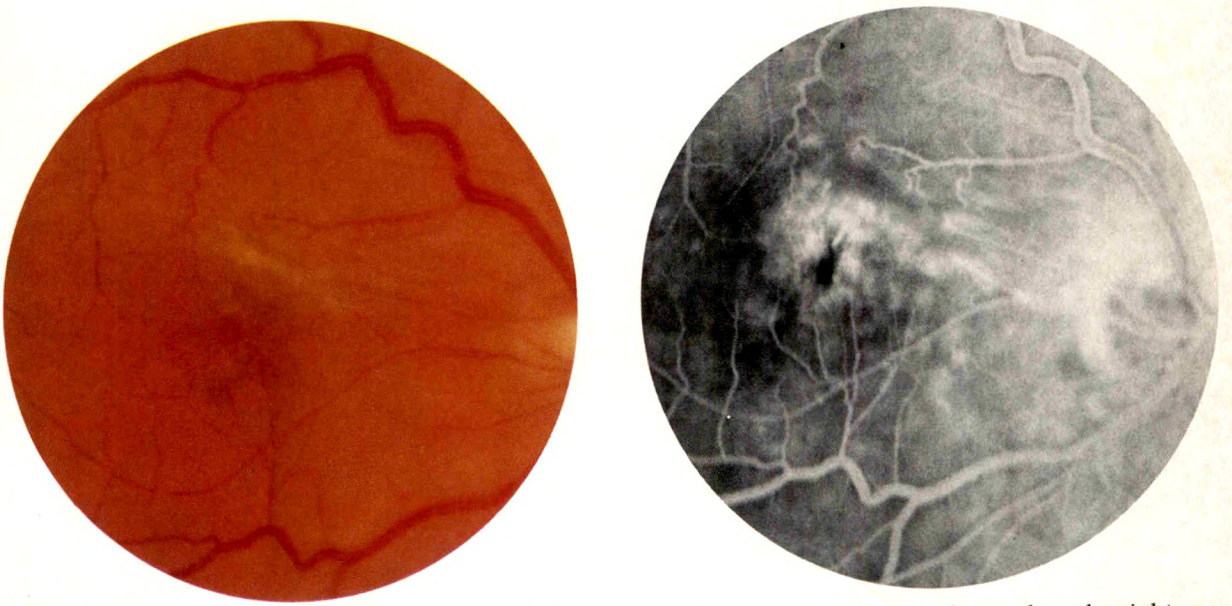


Fig. 9 (Michels and associates). Case 3. Left, One month after vitrectomy for macular pucker, the right eye demonstrated a persistent epimacular membrane. Visual acuity was 20/100. Right, Fluorescein angiogram shows persistent macular edema and no abnormalities at the level of the retinal pigment epithelium or choroid.

in the right eye were performed. On April 6, 1989, the visual acuity in the right eye was 20/100 and a persistent epiretinal membrane on the superotemporal macula that exerted traction on the fovea was noted (Fig. 9). On April 14, 1989, a repeat pars plana vitrectomy with epiretinal membrane dissection was performed. The epiretinal membrane adhered to the retina and fragmented while it was being removed. No intraoperative complications occurred. The Trek intraocular endoilluminator and light source were used. External illumination was provided by an operating microscope fitted with a 100-W halogen bulb transmitted with a fiberoptic cable. Total surgical time was two hours 25 minutes. The oxygen saturation was 99% and core temperature was 35.5 to 36.4 C.

Five days postoperatively, the visual acuity in the right eye was 20/70. The macula showed mild white opacification and edema of the outer retina involving the superior macula. On May 18, 1989, the visual acuity in the right eye was 20/80. Fundus examination disclosed a sharply demarcated area of hypopigmentation at the level of the pigment epithelium in the superonasal macula (Fig. 10). Fluorescein angiogra-

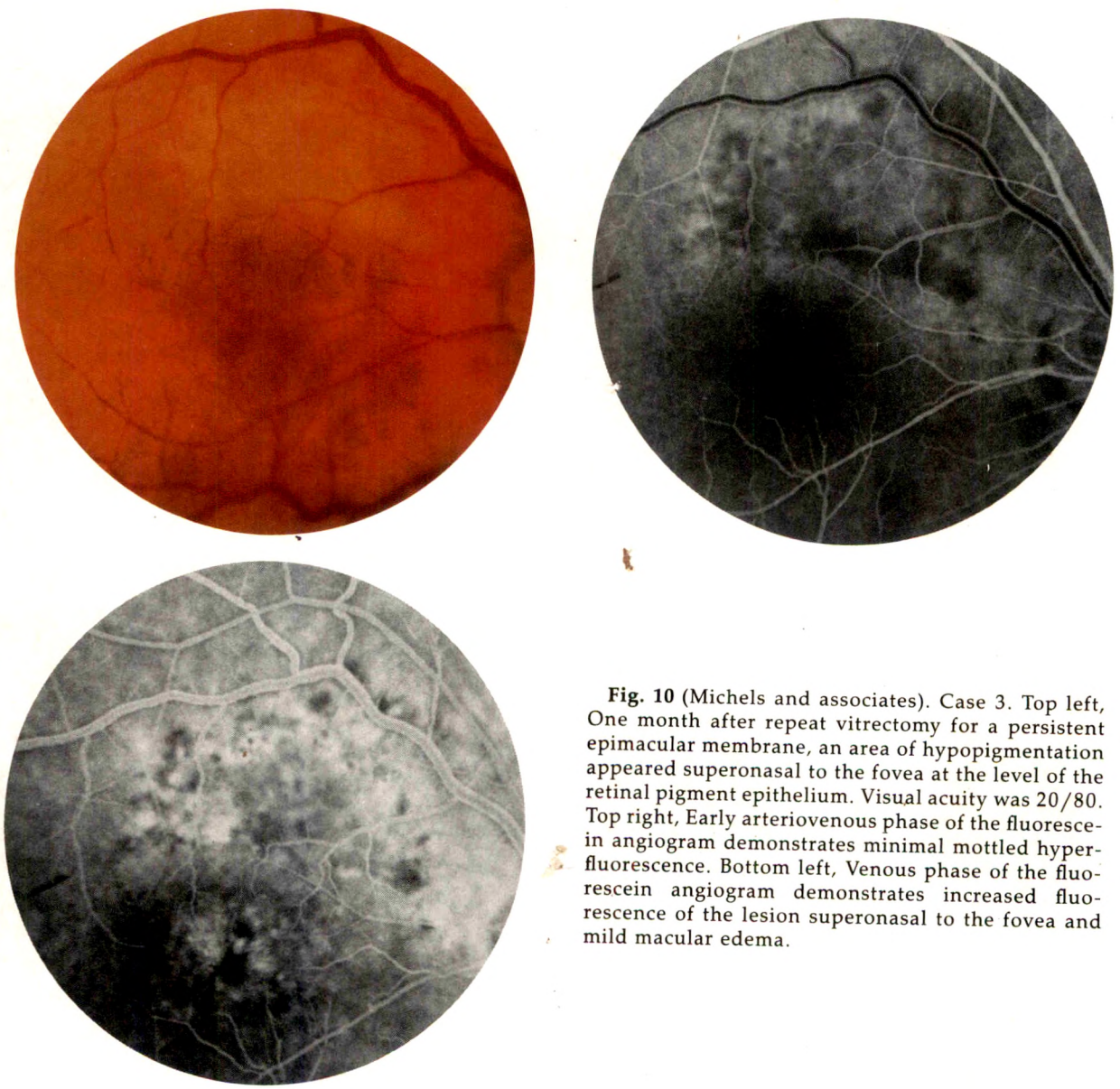


Fig. 10 (Michels and associates). Case 3. Top left, One month after repeat vitrectomy for a persistent epimacular membrane, an area of hypopigmentation appeared superonasal to the fovea at the level of the retinal pigment epithelium. Visual acuity was 20/80. Top right, Early arteriovenous phase of the fluorescein angiogram demonstrates minimal mottled hyperfluorescence. Bottom left, Venous phase of the fluorescein angiogram demonstrates increased fluorescence of the lesion superonasal to the fovea and mild macular edema.

phy disclosed mottled hyper- and hypofluorescence corresponding to the area of retinal pigment epithelial hypopigmentation seen clinically.

Results

The epiretinal membranes in the macular region in our cases were secondary to a rhegmatogenous retinal detachment in one eye, a posterior vitreous separation with the development of retinal tears in one eye, and acute retinal necrosis in one eye. Preoperatively, the visual acuity ranged from 20/100 to 20/200. Intraoperatively, the epiretinal membranes adhered to the retina and were difficult to remove in two of the three cases. In these two cases, the endoillumination was held close to the retina, and the surgical procedure was prolonged. Retinal exposure to the light of the operating microscope, however, was limited to approximately 20 minutes for standard opening and closing associated with a three-port vitrectomy. In all three cases, macular lesions consisting of white opacification of the outer retina were noted within one week postoperatively. These findings were not noted intraoperatively. The macula was edematous, and in one eye (Case 1) acute segmental retinal phlebitis was also present overlying the area of outer retinal opacification. The macular lesions were all sharply demarcated, irregularly oval to round, varied in size from 2 to 5 disk diameters, and involved the fovea in two eyes. Initially, the visual acuity decreased in two eyes and improved in one eye. With time, visual acuity improved in the eyes with initial postoperative decrease in vision. The visual acuity of one eye improved to substantially better than the preoperative value. The time to recovery of best visual acuity varied from three to 12 months. With time, the white opacification of outer retina changed and was characterized by mottling of the retinal pigment epithelium.

Discussion

In our three cases, the characteristic course of the macular lesion and its fluorescein angiographic features were typical of retinal phototoxicity.[2] Phototoxic lesions are typically noted clinically only several days after the light exposure as in our three cases. A discrete margin of retinal pigment epithelial hypopigmentation is noted to develop as the initial outer retinal whitening fades. Fluorescein angiography clearly demonstrates the area of retinal pigment epithelial disturbance, as early discrete hyperfluorescence throughout the area of mottled pigmentary change evolves to late staining but never leakage. In most cases, the pigment clumping results in a monotonous, diffuse mottled hyperfluorescence that can evolve into a target-like central clumping surrounded by hypopigmentation.

Typically, lesions caused by the operating microscope assume the shape of the light source used.[6] The lesion produced by tungsten filaments often assumes the oval shape of the filament, whereas fiberoptic systems often generate a round lesion.[1] These lesions tend to have sharply demarcated borders partly because of minimal ocular or light position change during anterior segment procedures. The size of the lesion is usually less than 1 to 2 disk diameters.

Our cases demonstrated the typical clinical and fluorescein angiographic features of operating microscope–induced retinal phototoxicity. The features that differentiate the lesions in our cases from the typical operating microscope–induced lesion are the size and shape of the lesions and the minimal exposure to light from the operating microscope. In all three cases, the lesions were markedly larger than would be expected with the operating microscope light source. In Case 2, a nearly round lesion was seen despite the use of a tungsten filament in the microscope light source, which should result in a lesion of much smaller and more rectangular dimensions. The lesions in our cases had marked pleomorphism, probably because of intraoperative alterations in illumination positioning in terms of proximity to the retinal surface as well as location of illumination, which is typical of surface-level vitrectomy, especially when it involves dissection of epiretinal membranes over a large area. The lesion in Case 3, however, had a fairly discrete epiretinal membrane above the fovea. Surface dissection involved a discrete area and the light exposure was likely limited largely to this area. This probably accounts for the comparatively discrete appearance of the phototoxic lesion. Similarly, anterior segment procedures which may result in operating microscope–induced retinal phototoxicity and experimental endoilluminator-induced retinal phototoxicity are characterized by minimal change in light

position and therefore may result in discrete lesions.[7]

Retinal phototoxicity is a function of the following three factors: wavelength of the light source, duration of exposure, and power level. Duration of exposure and power level determine total energy delivered to a target tissue.[8] For retinal phototoxicity to occur, energy must be transmitted to and absorbed by a target tissue. With an operating microscope, light is transmitted through the whole globe, a process that has been carefully studied. In the intact globe, reflection by and absorption in the tissues anterior to the retina protects the retina from the short-wavelength ultraviolet light and some of the blue visible light that is most efficient in inducing phototoxicity.[9,10]

With an endoilluminator, there is no absorption of damaging irradiation by anterior ocular structures once the vitreous is cleared of opacity. Fuller, Machemer, and Knighton[7] found that clinical phototoxicity can be seen after a 15-minute exposure and histologic damage can be noted after just a 10-minute exposure in owl monkeys. In their carefully controlled study, monkeys were exposed to between five and 30 minutes of endoillumination, and then studied by ophthalmoscopy, fluorescein angiography, and light and electron microscopy at several intervals after exposure. As is true of all cases of photochemical damage, lesions were not immediately apparent even after the 30-minute exposure, but could be seen as early as five hours after exposure. This observation is critical for the vitreoretinal surgeon who is accustomed to observing immediate thermal effects delivered by other forms of electromagnetic irradiation, such as the endolaser.[8]

Kuhn, Morris, and Massey[4] suggested that the danger of iatrogenic photic damage from the endoilluminator probe with subsequent visual impairment is greatest when vitrectomy is performed for epiretinal membrane dissection. They concluded that the problem is not widely recognized because the subtle changes clearly seen by fluorescein angiography are likely to be overlooked on ophthalmoscopy. We further suggest that many of the characteristic angiographic findings noted at the level of the retinal pigment epithelium may not be present when retinal phototoxicity occurs in detached retina, as has been experimentally demonstrated by Zilis and Machemer.[11] In this instance, damage to noncontiguous retinal pigment epithelium may not be seen even with fluorescein angiography.

Protection of the retina from endoilluminator-associated retinal phototoxicity is provided in part by macular xanthophyll. Jaffe and Wood[12] were the most recent to demonstrate this qualitatively. Our Case 2 demonstrates macular sparing that may be explained in part by the macular xanthophyll. Ham and associates[8] demonstrated a twofold threshold energy increase required to produce a foveal compared to a parafoveal lesion in monkeys.

Although no direct evidence links wavelength attenuation with reduction of endoilluminator-associated retinal phototoxicity, experimental work in phakic dogs[13] and rhesus monkeys[14] suggests that limitation of blue light exposure markedly reduces the incidence of indirect ophthalmoscope–induced and of operating microscope–induced retinal phototoxicity, respectively. Although Fuller, Machemer, and Knighton[7] documented less than 5% blue light output from their light pipe endoilluminator, and Meyers and Bonner[15] measured that the blue fraction is less than 3% of transmitted energy, both groups of authors emphasized that elimination of light less than 500 nm from fiberoptic endoilluminators may decrease the risk of retinal phototoxicity by tenfold. Experimental proof of the benefit of blue light filtration in the endoilluminator probe is lacking.

Other factors that are somewhat controllable are the power level of the light source and the exposure time. The currently popular cooler (and bluer) light sources, such as the xenon

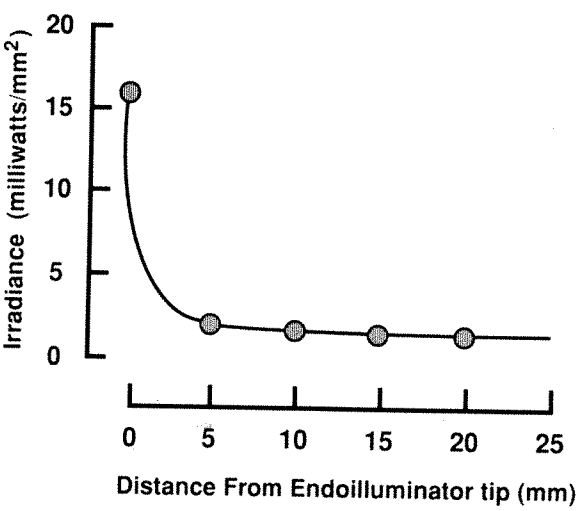


Fig. 11 (Michels and associates). Endoilluminator irradiance as a function of the distance from the light source (mW/mm^2) in air measured using the Trek endoilluminator and light source.

source, and the higher intensity often needed for video recording equipment need to be considered when performing a surgical procedure. Maximum output of the Trek endoilluminator and light source and the Grieshaber endoilluminator and light source was determined to be 15.6 and 18.0 mW/mm^2, respectively, using a silicone diode photodetector (UDT model 247) traceable to the National Bureau of Standards. Although power level is not often considered a flexible variable, it is noteworthy that the retinal irradiance value is inversely proportional to the square of the distance of the source light to the retinal surface.[16] Thus, moving the light source as far away from the retinal surface as is possible during noncritical periods of membrane dissection seems prudent (Fig. 11). With regard to exposure time, some investigators have advocated intermittent exposure as less likely to cause the same degree of damage as constant exposure for a given cumulative time period.[4] The importance of intermittent exposure is debatable. Data on brief intermittent exposures in pseudophakic primates[17] and phakic primates[18] contend that these exposures are cumulative and that intermittent intraoperative rest periods are unlikely to be protective.

There are two variables independent of the immediate ocular milieu that probably do have a role in retinal phototoxicity. System temperature has long been recognized as important in retinal phototoxicity. The idea that the photochemical process might be enhanced by increased core temperature was addressed and shown by Noell and associates.[19] Rinkoff and associates[20] demonstrated that cooling infusion fluid from 39 C to 29 C in rabbits in which vitrectomy had been performed while closely illuminating the retina with an endoilluminator increased the damage threshold time from 25 to 60 minutes. Although neither alteration of core temperature nor use of hypothermic infusion fluid has been studied in humans, it is prudent to avoid unnecessary increases in core or infusion fluid temperature.

The other variable not immediately associated with the globe is tissue oxygenation. Because the photochemical process is thought to result from the action of free radical and singlet oxygen moieties, high levels of inspired oxygen might decrease the threshold for phototoxicity. Jaffe and associates[21] studied the role of inspired oxygen in phakic rhesus monkeys exposed to operating microscope light under conditions of 21% FiO_2 and 99% FiO_2 and noted marked potentiation of phototoxic damage under conditions of increased oxygenation. Although oxygenation has not been directly studied under conditions of endoilluminator-related retinal phototoxicity, it seems prudent to avoid unnecessary oxygenation in patients undergoing a surgical procedure using the endoilluminator.

Endoilluminator-related retinal phototoxicity is a largely unrecognized, and partially preventable, sequela to certain cases of vitrectomy. Awareness of the potential for its occurrence and minimization of both intraocular and extraocular variables that may contribute to the process are advised.

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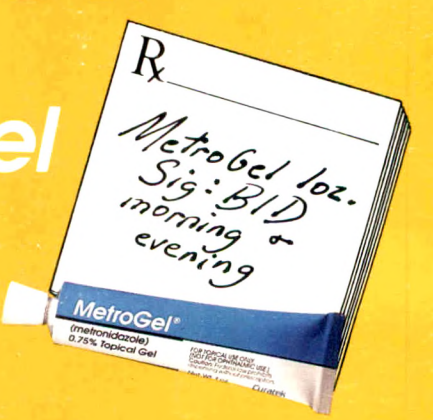
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Drug Interactions Drug interactions are less likely with topical administration but should be kept in mind when METROGEL is prescribed for patients who are receiving anticoagulant treatment. Oral metronidazole has been reported to potentiate the anticoagulant effect of coumarin and warfarin resulting in a prolongation of prothrombin time.

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Nursing Mothers Even though METROGEL blood levels are significantly lower than those achieved after oral metronidazole, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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Pattern Discrimination Perimetry in Patients With Glaucoma and Ocular Hypertension

Matthew J. Nutaitis, L.C.D.R., William C. Stewart, M.D., Dolores M. Kelly, B.S., Hurshell H. Hunt, Ph.D., and Matthew L. Severns, Ph.D.

We compared the results of the pattern discrimination perimeter to the program 30-2 on the Humphrey Field Analyzer (Humphrey, Inc., San Leandro, California) in 93 consecutive patients with ocular hypertension and glaucoma and 30 control patients. In 20 patients with ocular hypertension, a significantly greater number of glaucomatous defects were noted on pattern discrimination perimetry (ten patients) than on the program 30-2 (two patients) ($P < .05$, Wilcoxon signed rank test). The diversity in diagnoses found on pattern discrimination testing was not explained by age, intraocular pressure, refraction, number of glaucoma medicines, race, presence of vascular disease, optic disk status, or pupil size. In contrast, in 73 patients with glaucoma no statistical difference in the severity of diagnoses was noted between perimeters ($P > .05$, Wilcoxon signed rank test). These results suggest the potential value of pattern discrimination perimetry as a visual function test in patients with glaucoma and in defining subsets of patients with ocular hypertension not found with conventional automated perimetry.

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From the Glaucoma Service at the Department of Ophthalmology (Drs. Nutaitis and Stewart, and Ms. Kelley), and the Department of Biostatistics, Epidemiology and System Sciences (Dr. Hunt), Medical University of South Carolina, Charleston, South Carolina; and the Wilmer Eye Institute (Dr. Severns), Johns Hopkins University School of Medicine, Baltimore, Maryland. This study was supported in part by unrestricted grants from Research to Prevent Blindness, Inc., New York, New York. Dr. Severns is an employee of LKC Technologies, Inc., Gaithersburg, Maryland.

The opinions expressed herein are those of the authors and are not official opinions of the Department of the Navy.

Reprint requests to William C. Stewart, M.D., Medical University of South Carolina, Storm Eye Institute, 171 Ashley Ave., Charleston, SC 29425-2236.

VISUAL FIELD TESTING is performed in patients with increased intraocular pressure to determine the amount of damage to the visual system. Most perimeters currently available rely on a uniform white stimulus projected on a white background to assess visual function. Unfortunately, this stimulus detects glaucomatous changes only after extensive damage to the optic nerve head has already been sustained.[1]

The pattern discrimination perimeter, which recently has been described, requires recognition of a pattern stimulus, which may have the advantage of earlier detection of glaucomatous damage than conventional automated perimetry.[1] We evaluated the use of pattern discrimination perimetry compared to automated perimetry in routine testing of patients with ocular hypertension or glaucoma.

Subjects and Methods

We included in this study consecutively tested patients with glaucoma and ocular hypertension who were examined with automated perimetry at the Storm Eye Institute at the Medical University of South Carolina. Patients with glaucoma were defined as having typical glaucomatous-appearing optic disk damage and a history of an intraocular pressure greater than 21 mm Hg with or without visual field damage. Patients with ocular hypertension were defined as having a history of an increased intraocular pressure greater than 21 mm Hg without clinical signs of optic disk damage. We excluded patients with marked neurologic and retinal disease and those who were unable to complete a visual field examination. If both eyes were tested, only one eye was randomly chosen to be included in this study. A control group of normal individuals who had one eye randomly chosen to be examined also was included in this study.

Each subject was tested with the Humphrey Field Analyzer (Humphrey, Inc., San Leandro, California), a fully automated perimeter with a 330-mm bowl that projects a uniform white stimulus on a white background. Subjects were examined with the program 30-2, which uses a staircase technique to determine threshold at 76 locations spaced 6 degrees apart and offset symmetrically across the vertical and horizontal midlines within the central 30 degrees (Fig. 1).

After testing with the Humphrey Field Analyzer, subjects also were examined with the pattern discrimination perimeter (LKC Technologies, Inc., Gaithersburg, Maryland), described previously.[1] This perimeter's computer generates a display on a 5-inch television monitor. An optical system relays this image to the eye while providing refractive correction and eccentricity-dependent magnification such that the image appears to be on the surface of a bowl located at optical infinity. The graphics display produces black or white pixels, 640 in number horizontally and 480 vertically. The perimeter has a 30-degree field of view. A fixation target is present in the middle of the graphic display, and fixation is checked by a technician who uses a separate television monitor.

Using the pattern discrimination perimeter, we tested 32 locations within the arcuate area of the visual field at the same locations tested by the program 30-2 on the Humphrey Field Analyzer. Testing was limited to the arcuate area to shorten the test time (approximately 15 minutes) and because of previous reports of its importance in glaucoma diagnosis[2] (Fig. 2).

				1	0	-3	-6								
			-2	-5	-5	-3	-1	-2							
		-4	-1	-3	-3	-4	-3	-1	-1						
	-3	-6	-5	-4	-5	-4	-2	2	-3	0					
	0	-5	-3	-1	-1	-1	0		1	-3					
-19	-26	-32	-33	-1		25	-28		-7	-8					
-4	-6	-20	-17	-33		-9	-13	-6	-7	-6					
	-2	-8	-5	-16		-4	-9	-4	-2						
		-5	-7	-6		-5	-7	-4							
			-5	-3		-4	-6								

Fig. 1 (Nutaitis and associates). A right-eye visual field using the program 30-2 of the Humphrey Field Analyzer from a patient with glaucoma showing inferior arcuate changes typical for glaucoma on the depth defect printout. Locations are spaced 6 degrees apart and blind spot values were not included.

	98*	67	83	78		
77	84*	72	76	77	88*	
85*	71	64	82*	91*	73	
69	73	71	98*	85*	63	
73	72	95*	83*	68	80*	
	68	56	64	63		

Fig. 2 (Nutaitis and associates). Visual field of the same eye as in Figure 1 using the pattern discrimination perimeter with threshold levels within the arcuate area. Asterisks indicate abnormally depressed locations and show a stippled pattern typical for patients with glaucoma undergoing pattern discrimination testing. Locations are spaced 6 degrees apart and the blind spot was not tested.

The pattern discrimination perimeter tests the visual field by presenting a square checkerboard stimulus of alternating black and white pixels on a background of randomly arranged black and white pixels. Stimulus recognition is made more difficult by decreasing, by an arithmetic progression, the percentage of the stimulus that is composed of the alternating black and white pixels and increasing the percentage of the stimulus that has the randomly arranged pixel background (spatial coherence).

The perimeter determines in a staircase fashion the lowest spatial coherence the patient is able to discern at each location (pattern discrimination threshold) (Fig. 3). For this study, the initial stimulus was presented at 60% spatial coherence. If the subject perceived the initial stimulus, the spatial coherence was reduced in 4% steps until the stimulus was not visualized. The spatial coherence then was increased by 2% steps until observed again. The spatial coherence then was reduced by 1% steps until the subject failed again to see the stimulus, which determined the pattern discrimination threshold. In contrast, if a subject failed to visualize the initial stimulus, then the inverse progression of equal percentage steps was performed to determine threshold.

In this study, each stimulus was presented for 0.6 second and the time interval used between stimulus presentations was 0.3 second. The size of the stimulus was 20 pixels horizontally and 20 pixels vertically. However, the pixel size depended on the distance from fixation. Within 5 degrees from fixation, the pixel size was 7.5

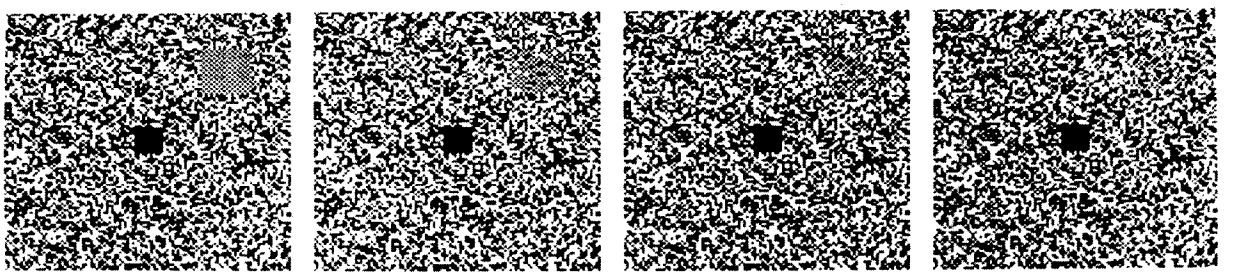


Fig. 3 (Nutaitis and associates). Schematic of the pattern discrimination stimulus showing a decreasing percentage of spatial coherence (left to right) of nonrandom black and white pixels projected on a randomly arranged black and white pixel background. The stimulus is located to the upper right of the black central fixation target.

minutes; between 5 degrees and 13 degrees from fixation, the pixel size was 15 minutes, whereas further than 13 degrees from fixation, the pixel size was 22.5 minutes. The background pattern of nonrandom pixels was updated four times per second. These variables were chosen on the basis of findings from our laboratory (Nutaitis and associates, unpublished data, 1991), which indicated these variables provided the most reproducible visual stimulus at the lowest spatial coherence.

Each visual field was interpreted independently by two of us (M.J.N., W.C.S.). Also, the pattern discrimination field and the program 30-2 field were interpreted independently from each other. After each visual field was interpreted, it was categorized as being within normal limits or having either a specific (probably a glaucoma-related change) or nonspecific (not definitely a pathologic change) visual field defect.

Criteria used in this study for interpreting the program 30-2 visual fields have been described previously[3,4] and reflect the global diagnoses commonly used for automated perimetry. Criteria used in this study for interpreting the pattern discrimination visual fields were based on previous data that individual locations within the central 30 degrees have an equal diagnostic value in determining a defect.[1] The number of abnormal locations used to define an abnormality with the pattern discrimination perimeter was adjusted so the number of specific and nonspecific defects was similar to the program 30-2 visual field within the control population. This definition stipulated that eight or more locations defined a specific defect and six to seven abnormal locations defined a nonspecific defect with the pattern discrimination perimeter. This definition provided a specificity of 93% in excluding a probable glaucomatous change, which is similar to past information regarding the specificity of the Humphrey Field Analyzer.[5] An abnormal location itself was defined as having a pattern discrimination threshold greater than two standard deviations from the mean threshold of the control population at each tested location.

After each visual field was defined (normal, nonspecific defect, or specific defect), the program 30-2 and pattern discrimination visual fields were compared as to the severity of the defects by using the Wilcoxon signed rank test separately for the glaucoma, ocular hypertension, and control groups. If a significant difference in diagnoses was observed, further statistical evaluation was performed to attempt to explain the diversity. This evaluation included Goldmann applanation tonometry and patient age analyzed by a Student's *t*-test, and pupil size, refraction, number of glaucoma medicines, cup/disk ratio, race, and existence of vascular disease analyzed by a chi-square test.

We also evaluated the similarity of the defect location between the two perimeters. To do this we determined which hemifield (superior or inferior) showed the greatest sensitivity loss for each patient for both perimeters separately. The results from both perimeters then were compared for each eye tested.

Results

We included in this study 93 eyes (39 left eyes and 54 right eyes) of 93 consecutive patients with glaucoma or ocular hypertension who

were examined at the Medical University of South Carolina. The patients had an average age of 66.8 ± 14 years.

Thirty control patients (15 right and 15 left randomly tested eyes) who had an average age of 32.4 ± 10 years were included in this study. Two subjects had a specific defect and two had a nonspecific defect on both the program 30-2 and the pattern discrimination perimeter, which was not a statistically significant difference ($P > .05$).

The diagnosis agreed between the two perimeters in 55 of the 73 patients (75.3%; 73 eyes) with glaucoma. Five of 73 eyes (6.8%) showed a more severe defect with the pattern discrimination perimeter and 13 of 73 eyes (17.8%) showed a more severe defect with the program 30-2. This was not a statistically significant difference ($P > .05$).

The diagnosis was normal on both the pattern discrimination perimeter and the program 30-2 in seven of 20 patients (35.0%; 20 eyes) with ocular hypertension. Both programs showed a specific defect in one eye (5%). However, in three eyes (15%), the pattern discrimination perimeter visual fields were normal, whereas the program 30-2 showed either a nonspecific (two eyes) or a specific (one eye) defect. In the other nine eyes (45.0%), the pattern discrimination perimeter showed a specific defect, whereas the visual field of the program 30-2 was normal. The difference in diagnoses between perimeters was statistically significant ($P < .05$). The diversity in diagnoses between patients with ocular hypertension who showed a specific defect and those who were normal on pattern discrimination perimetry was not explained by differences in the intraocular pressure, age, refraction, pupil size, optic nerve, race, presence of vascular disease, or number of glaucoma medicines ($P > .05$).

In comparing defect location between perimeters, 36 eyes (49.4%) differed in the hemifield (inferior or superior) with the greatest sensitivity loss (Figs. 1 and 2). Most defects were observed in the superior hemifield with both perimeters.

Discussion

The diagnosis of glaucoma depends on observing an increased intraocular pressure associated with typical glaucomatous-appearing changes in the optic nerve head and on visual function testing. The most common visual function test used to diagnose and monitor patients with glaucoma is automated perimetry, which projects a uniform white stimulus on a white background to determine a differential light threshold.[2] However, automated perimetry does not detect early glaucomatous damage.[6] Electrophysiologic studies have shown that individual ganglion cells can respond to light intensities close to normal differential light threshold levels,[7,8] probably because retinal ganglion cell receptive fields overlap extensively. Consequently, many ganglion cells must be lost before a scotoma appears that can be detected by changes in the differential light threshold.

A stimulus that necessitates form recognition, however, might require a greater percentage of intact ganglion cells and may be more sensitive to glaucomatous damage than stimulus recognition based on light sensitivity.[1] The pattern discrimination perimeter is based on the theory that visual perception by the retina is coded by the weighted responses of all ganglion cells whose receptive fields cover that location. Consequently, early ganglion cell loss might disturb the coding of the relative position of perceived objects before changes in differential light threshold become apparent.[1]

Compared with automated perimetry, pattern discrimination testing at individual locations within the central 30 degrees tended to be more sensitive in diagnosing ocular hypertension and equally sensitive in diagnosing glaucoma.[1,9]

We compared pattern discrimination perimetry and conventional automated perimetry in patients with glaucoma and ocular hypertension by using global diagnostic criteria that might be applied clinically.

This study showed that in patients with ocular hypertension, a statistically greater number of abnormal tests were identified with the pattern discrimination perimeter than the program 30-2. One half of the patients with ocular hypertension showed numerous (greater than 11) abnormal locations on pattern discrimination perimetry while the other half showed few if any defects. Few defects were noted with the program 30-2. The difference in the pattern discrimination test results between groups of normal and abnormal patients was not explained on the basis of intraocular pressure, pupillary dilation, refraction, age, number of glaucoma medicines, race, cup/disk ratio, family history of glaucoma, or the presence of vascular disease. These results are consistent with the theory that the pattern discrimination stim-

ulus requires a greater number of intact ganglion cells to be observed, and potentially may show visual function damage earlier, than automated perimetry.[1]

In this study, the separation of patients with glaucoma from normal individuals was similar using both the pattern discrimination perimeter and the program 30-2. However, the involved area of the visual field on the program 30-2 differed from that observed on pattern discrimination testing in half of the patients. The reason for this difference was not explained by our results, but is consistent with the hypothesis that the pattern discrimination perimeter may measure a different aspect of a visual system than automated perimetry.[1]

Previous information has indicated that no location more than another signifies a glaucomatous defect in pattern discrimination testing. Consequently, we based the severity of the diagnosis only on the number of locations. This diagnostic approach differs from conventional automated perimetry testing, in which abnormal locations within the arcuate area and adjacent abnormal locations more strongly indicate a glaucomatous defect.[10,11] Although the scale we used was relative, increasing or decreasing the number of locations that indicated a defect did not improve the relative sensitivity and specificity of the pattern discrimination examination in our patients. We defined the number of locations that determined a defect to provide a specificity of 93%, which is similar to conventional automated perimetry.[5] To save time on the pattern discrimination testing, we did not test the peripheral visual field, which previous studies have indicated might be useful diagnostically.[1,9] Consequently, the peripheral visual field may be worthwhile for future study in pattern discrimination testing.

This study suggests that the separation of patients with glaucoma from normal subjects in pattern discrimination perimetry is similar to that in conventional perimetry. However, in patients with ocular hypertension, the pattern discrimination perimeter identifies subsets of patients either with or without a visual function defect. These diagnostic subsets may prove useful in the future as an early diagnostic and prognostic determinant for glaucoma.

This study was not designed to show a definite clinical importance or reproducibility of the defects found in patients with ocular hypertension on pattern discrimination testing. Long-term follow-up and further evaluation of the pattern discrimination perimeter is required to understand its potential clinical usefulness. Also, variables of the pattern discrimination perimeter (that is, pixel size, stimulus duration, background update time, and stimulus size) may be worthy of further evaluation to determine if more important clinical information is gained.

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Long-term and Short-term Fluctuation in Pattern Discrimination Perimetry

William C. Stewart, M.D., Dolores M. Kelly, B.S., and Hurshell H. Hunt, Ph.D.

We studied threshold fluctuation with the pattern discrimination perimeter in 24 healthy subjects at 56 locations within the central 30 degrees. This perimeter evaluates a subject's ability to discriminate a patterned stimulus measured by a percentage scale. We found an intraindividual fluctuation of 10.52% and an interindividual fluctuation of 8.78%. A statistically increased intraindividual, but not interindividual fluctuation was noted with increasing eccentricity from fixation ($P < .05$, Bartlett's test). However, no correlation in fluctuation was noted with advancing age or increasing false-positive errors ($P > .05$, correlation coefficient). Also, no difference in fluctuation between superior or inferior hemifields was observed ($P > .05$, Student's t-test). The average threshold across all subjects was 54.3%, which provided an upper limit of normal, two standard deviations from the mean, of less than 80% for most locations. This study indicates that fluctuation should be considered when interpreting pattern discrimination fields, but that the extent of fluctuation generally allows for an adequate separation between normal and abnormal measurements.

THE PATTERN DISCRIMINATION perimeter, which requires recognition of a patterned stimulus instead of a uniform white target on a white background as in automated perimetry, was recently developed. Because discerning a patterned stimulus may require a greater number of intact ganglion cells than a uniform white stimulus, the pattern discrimination perimeter potentially may detect damage within the visual system earlier than automated perimetry.[1-5]

In automated perimetry, a normal fluctuation exists between measured threshold values.[6-8] This fluctuation must be considered when interpreting automated visual fields.[6-8] We evaluated the extent of both the intra- and interindividual fluctuation in pattern discrimination testing. We also examined for associated factors in pattern discrimination testing that might influence fluctuation.

Subjects and Methods

We included in this study 24 healthy individuals who worked or studied at the Medical University of South Carolina. One eye from each subject was randomly chosen to be tested. Each individual had no history of glaucoma, 20/20 Snellen visual acuity, and a pupillary diameter of 3 mm or greater. Each subject was tested with their best-corrected visual acuity. We excluded from this study any individual who had a history of an eye disease that might obscure the ocular media or disturb visual function.

Each subject was tested with the Humphrey Field Analyzer (Humphrey, Inc., San Leandro, California), a fully automated perimeter with a 330-mm bowl. This perimeter projects a uniform white stimulus on a white background. Each patient was examined with the program 30-2, which uses a staircase technique to determine threshold at 76 locations within the central 30 degrees, spaced 6 degrees apart, equally offset across the horizontal and vertical midlines. Testing with conventional automated perimetry was performed to assure normalcy of the visual field for each subject.

After testing with the Humphrey Field Analyzer, subjects were tested with the pattern

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From the Glaucoma Service at the Department of Ophthalmology (Dr. Stewart and Ms. Kelly) and the Department of Biostatistics, Epidemiology and System Sciences (Dr. Hunt), Medical University of South Carolina, Charleston, South Carolina. This study was supported in part by unrestricted grants from Research to Prevent Blindness, Inc., New York, New York.

Reprint requests to William C. Stewart, M.D., Storm Eye Institute, Medical University of South Carolina, 171 Ashley Ave., Charleston, SC 29425-2236.

discrimination perimeter (LKC Technologies, Gaithersburg, Maryland). This perimeter's computer generates a square stimulus of alternating black and white pixels on a background of randomly arranged black and white pixels. The details of the perimeter hardware and visual field testing method have been described previously.[9] In this study, each stimulus was presented for 0.6 second and a 0.3-second time interval was used between stimulus presentations. The stimulus comprised 20 pixels horizontally and 20 pixels vertically. The size of the pixel depended on the distance from fixation. Within 13 degrees from fixation, the pixel size was 15 minutes, whereas outside 13 degrees from fixation, the pixel size was 22.5 minutes. The background pattern of nonrandomly arranged pixels was updated four times per second. These variables were based on findings from our laboratory (Stewart, Kelly, and Hunt, unpublished data, 1991), which indicated these variables provided the best-visualized and most reproducible stimuli.

Initially, each subject was tested with a short practice program on the pattern discrimination perimeter. We then tested 56 locations twice within the central 30 degrees with a 6-degree grid equally offset across the vertical and horizontal midlines (Fig. 2). Left-eye tests were converted to right-eye tests for data analysis. Twelve patients were randomly chosen to be tested twice on the same day and the other 12 patients were tested once on each of two separate days within a two-month time period.

The short-term intraindividual fluctuation was determined at each location by calculating the square root of the variance of the pattern discrimination threshold between tests of subjects tested on the same day. The total intraindividual fluctuation was determined at each location from the square root of the variance of the pattern discrimination threshold between tests from subjects tested on separate days. The average total and short-term fluctuation also were determined across all locations. The difference between these variances provided an estimate of the homogeneous long-term intraindividual fluctuation.

The interindividual fluctuation was determined by taking the square root of the variance of the average pattern discrimination threshold between each subject at each location. The average interindividual fluctuation also was determined across all locations. Locations not visualized by subjects were not included in the estimates for the variance components.

The influence of age and the percentage of false-positive errors on fluctuation was assessed by using a correlation coefficient for the short-term and total intraindividual fluctuation. The influence of eccentricity between 0 degrees and 10 degrees, between 10 degrees and 20 degrees, and between 20 degrees and 30 degrees from fixation was determined by a Bartlett's test for the short-term and total intraindividual fluctuation and for the interindividual fluctuation. Also, a significant difference in fluctuation between the superior and inferior hemifields was determined by an F-distribution test for the short-term and total intraindividual and interindividual fluctuation.

An upper limit of normal for the pattern discrimination threshold at each location was predicted. This limit was calculated by taking two standard deviations (using the total intraindividual fluctuation) added to the average pattern discrimination threshold at each location. Also, the average threshold across all locations was determined separately for subjects tested on the same and different days and a statistical difference was analyzed by using a Student's *t*-test.

The presence of a learning effect was ascertained separately in subjects tested on the same and different days. This test was performed by using a paired *t*-test to determine if a statistical difference existed between tests for the average pattern discrimination threshold, as well as the percentage of false-positive errors.

Results

Twenty-four subjects were included in this study. The 12 subjects included in the group tested on separate days had an average age of 25.3 ± 3.2 years (range, 22 to 33 years). Six were men and six were women. The average threshold value across all locations and subjects was 52.6% ± 5.0%. The 12 subjects in the group tested on the same day had an average age of 34.9 ± 8.5 years (range, 21 to 48 years). Three were men and nine were women. The average threshold across all locations and subjects was 56.0% ± 6.0%. The difference in threshold was not statistically significant between groups ($P > .05$).

The short-term intraindividual component was 9.52%, the homogeneous long-term intraindividual component was 4.47%, and the total intraindividual fluctuation was 10.53%. The

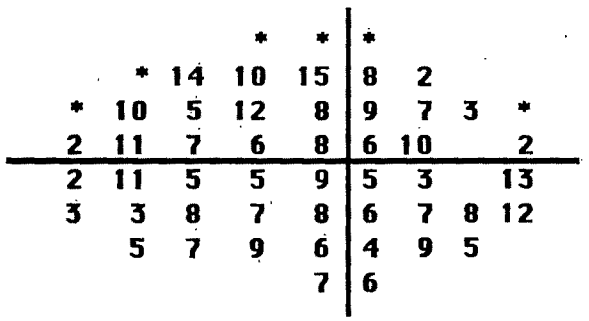


Fig. 1 (Stewart, Kelly, and Hunt). Pointwise intraindividual short-term fluctuation. (Locations are 6 degrees apart and numbers are in percentage points. Asterisks indicate unseen locations.)

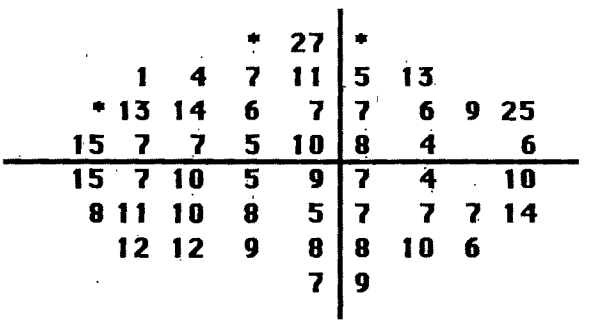


Fig. 2 (Stewart, Kelly, and Hunt). Pointwise intraindividual total fluctuation. (Locations are 6 degrees apart and numbers are in percentage points. Asterisks indicate unseen locations.)

pointwise short-term intraindividual fluctuation (Fig. 1) and the pointwise total intraindividual fluctuation (Fig. 2) were determined. The pointwise fluctuation tended to be slightly greater in the superior hemifield for short-term fluctuation, but did not reach statistical significance for either short-term or total intraindividual fluctuation ($P > .05$).

A statistically significant increase in total intraindividual fluctuation was noted with increasing eccentricity ($P < .05$), but not for short-term fluctuation ($P > .05$). No correlation with total ($\rho = -0.2300$) or short-term fluctuation ($\rho = 0.3502$) was noted with age ($P > .05$). Also no correlation with the total ($\rho = 0.2838$) or short-term fluctuation ($\rho = 0.0412$) was noted with the number of false-positive responses ($P > .05$).

The pointwise interindividual fluctuation was determined (Fig. 3). The overall interindividual fluctuation was 8.78%. No difference in fluctuation was observed between the superior and inferior hemifields or with increasing eccentricity from fixation ($P > .05$).

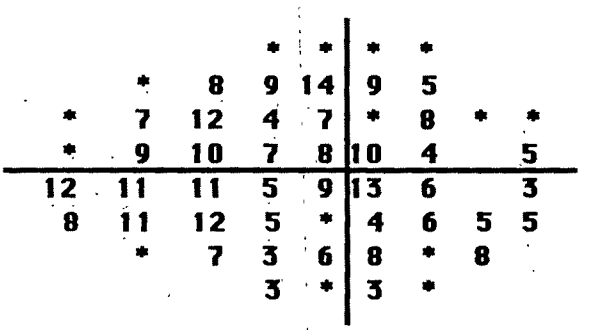


Fig. 3 (Stewart, Kelly, and Hunt). Pointwise interindividual fluctuation. (Locations are 6 degrees apart and numbers are in percentage points. Asterisks indicate unseen locations.)

The average pointwise pattern discrimination threshold values across all subjects was determined (Fig. 4). When two standard deviations from the mean were used for the total intraindividual threshold, most locations remained less than 80%.

In subjects tested on separate days to determine a learning effect, an improvement in the average pattern discrimination threshold of 54.2% to 51.0% ($P > .05$) was noted, which was not a statistically significant change. However, in subjects retested on the same day, a statistically significant improvement of 57.5% to 54.5% in the average pattern discrimination threshold was noted ($P < .05$).

The average false-positive response was decreased from 19.8% to 19.3% for the subjects tested on separate days, which was not a statistically significant difference. The average false-positive response decreased from 9.2% to 7.1% on repeat testing for subjects examined on the

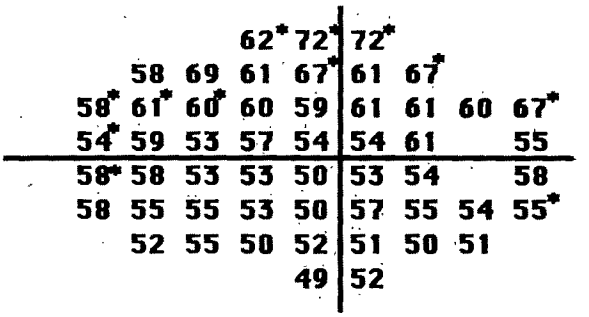


Fig. 4 (Stewart, Kelly, and Hunt). Average pointwise threshold values across all subjects. (Locations are 6 degrees apart and numbers are in percentage points. Asterisks indicate locations where the range of normal is above the level of 80% spatial coherence.)

same day, which was not reduced statistically on repeat testing ($P > .05$).

No specific nerve fiber layer or neurologic defects were noted for any subject when tested with the program 30-2 on the Humphrey Field Analyzer.

Discussion

In conventional automated perimetry, an expected fluctuation exists in repeated measurements for the differential light threshold.[6-8]

This fluctuation is important because it limits the accuracy of individual measurements for the differential light threshold.[6] In conventional automated perimetry, the expected fluctuation in normal subjects is increased in patients with ocular hypertension, glaucoma,[10] and in areas of decreased retinal sensitivity.[11] Also, increased fluctuation has been noted when using a mesopic background illumination[12] or a small Goldmann stimulus size (I or II),[13] as compared to the low photopic illumination or a stimulus size III typically used in automated perimetry. Additionally, increasing eccentricity from fixation has been associated with greater differential light threshold fluctuation.[14]

We evaluated the extent of intra- and interindividual fluctuation in testing normal subjects with pattern discrimination perimetry.

This study found that a normal fluctuation may be expected in the pattern discrimination threshold between tests taken by the same individual, as well as among individuals. However, the extent of fluctuation observed in this study indicated that an adequate normal and abnormal range of threshold values can be established in pattern discrimination testing. If two standard deviations from the mean threshold level are considered as the upper limit of normal, as has been used in automated perimetry,[15] then approximately a 20-percentage point range exists for most locations (between 80% and 100%) in which an abnormality may be diagnosed. Because a small learning effect was noted in our subjects, despite a practice examination, the normal range for the pattern discrimination threshold may be reduced with further testing.

Direct comparison of the fluctuation with pattern discrimination perimetry with the fluctuation with conventional automated perimetry is difficult because pattern discrimination perimetry uses a linear percentage scale to measure a pattern discrimination threshold, whereas conventional automated perimetry uses a relative log-based scale (decibels) to measure a differential light threshold. However, factors that influence fluctuation may be compared. In pattern discrimination testing, age may not be an important influence, whereas several investigators have shown this to be important in conventional automated perimetry.[16,17] However, age was not excluded as being significant in pattern discrimination testing because most of the subjects included in this study were relatively young.

Eccentricity was important in pattern discrimination perimetry when total fluctuation was considered, but not with short-term fluctuation, which was similar to findings in automated perimetry.[18] Also, the percentage of false-positive errors was shown not to influence pattern discrimination testing as opposed to conventional automated perimetry, in which the fluctuation in the mean defect may be significantly increased in unreliable patients.[18] No differences in fluctuation were observed between the superior and inferior hemifields, which was consistent with conventional automated perimetry.[18]

This study suggests that considering fluctuation is important in interpreting pattern discrimination visual fields. Also, an adequate separation from normal threshold values exists at most locations, despite threshold fluctuation, from which an abnormality may be diagnosed.

Further studies with the pattern discrimination perimeter are needed to determine normal threshold values across a large sample size of individuals in diverse age groups. Fluctuation and mean threshold values may differ across age groups and might influence how pattern discrimination fields are interpreted.

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OPHTHALMIC MINIATURE

But those colors! Pea-soup green. Sunflower yellow. Magenta. Chartreuse. Her favorite combination was purple and burnt sienna. Tom had a theory that there was something wrong with the rods and cones in her eyes.

Robert Plunket, *Love Junkie*
New York, Harper Collins Publishers, 1992, p. 37–38

Vagal Responses to Adjustable Sutures in Strabismus Correction

H. Sprague Eustis, M.D., Clement C. Eiswirth, M.D., and David R. Smith, M.D.

The oculocardiac reflex is a recognized complication of ocular stimulation, precipitated most commonly by traction on the extraocular muscles. To determine the true incidence of occurrence of the oculocardiac reflex during suture adjustments, 20 patients undergoing suture adjustment were monitored for blood pressure, heart rate, and rhythm abnormalities during the suture adjustment. A control group of ten patients with strabismus were studied postoperatively for comparison. Thirteen study patients and two control patients were noted to have a vagal response ($P < .001$). The most common response noted was a decrease in heart rate in 15 patients. Only two patients were symptomatic during vagal response (one patient became light-headed and another had an episode of nausea and vomiting). Suture adjustment was found to be the most common triggering event in precipitating vagal responses. Surgeons performing suture adjustment in strabismus correction should be cognizant of vagal responses so that they may properly inform patients of this possibility and take steps to minimize its occurrence.

DESCRIBED in 1975 by Jampolsky,[1] the adjustable suture method is recognized as a safe and useful adjunct in strabismus correction. By manipulating the position of the operated-on muscle when the patient has awakened, strabismus surgeons are better able to obtain a desirable alignment. Using this technique, the reoperation rate for strabismus has been reduced to approximately 10% in even the most difficult cases.[2]

The oculocardiac reflex is a well-described phenomenon precipitated by ocular stimulation, especially traction on the extraocular muscles. In two large series of patients undergoing strabismus correction, the intraoperative incidence of oculocardiac reflex during traction on extraocular muscles was 56%[3] and 68%.[4] Because the adjustable suture technique allows the surgeon to exert marked traction on the extraocular muscles, it is not uncommon to encounter the oculocardiac reflex during suture adjustment. Isenberg and Blechman[5] in 1982 described the oculocardiac reflex during manipulation of adjustable sutures. In 1986, Flynn[6] estimated that the incidence of the reflex occurring during suture adjustment was probably low. In 1987, Vrabec, Preslan, and Kushner[7] supported this belief with a prospective study of 44 patients undergoing suture adjustment in strabismus correction. During suture adjustment, two of 44 patients (4.5%) had bradycardia, defined as a decrease in heart rate of 10% below normal. In the Vrabec, Preslan, and Kushner study,[7] however, a digital pulse meter was the only means of patient monitoring; no electrocardiographic or blood pressure monitoring was performed. Therefore, the dysrhythmias and decreases in blood pressure that can occur with a vagal response would not have been detected.

We conducted this study to identify the true incidence of vagal responses occurring during suture adjustment and to determine whether these responses are oculocardiac reflexes or are vasovagal in origin. We also attempted to categorize the responses by simultaneous blood pressure, electrocardiographic, and heart rate monitoring. We hoped to identify which steps in the suture adjustment are important in eliciting the reflex.

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From the Department of Ophthalmology, Ochsner Clinic and Alton Ochsner Medical Foundation, New Orleans, Louisiana (Dr. Eustis); Gulf South Heart Institute, East Jefferson General Hospital, New Orleans, Louisiana (Dr. Eiswirth); and Department of Ophthalmology, University of Toronto, Hospital for Sick Children, Toronto, Ontario, Canada (Dr. Smith).

Reprint requests to H. Sprague Eustis, M.D., Ochsner Clinic, 1514 Jefferson Hwy., New Orleans, LA 70121.

Patients and Methods

From June 1986 through January 1988, all patients undergoing suture adjustment in strabismus correction were considered for inclusion in the study. Patients were excluded when monitoring equipment was not available at the time of the suture adjustment.

Of the 20 patients included, 18 had induction of general anesthesia and two had injection of retrobulbar or peribulbar anesthetic. The preoperative medication and the intraoperative anesthetic management varied depending on the anesthesiologist assigned to the case. In all cases, droperidol and atropine sulfate were given shortly before anesthetic induction. Four to six hours postoperatively, patients were transferred to the clinic area where the postoperative adjustment was performed. Before any manipulation of the eye, baseline heart rate, blood pressure, and electrocardiograms were obtained. Blood pressure readings were obtained at one-minute intervals using the Dinamap automated blood pressure machine (Johnson & Johnson Co., models 1846SX and 1846SX/P, Critikon, Inc., Tampa, Florida), and heart rate and rhythm were continuously assessed by the electrocardiography. Notations were made on both the rhythm strips and blood pressure readouts so that the exact cardiovascular status could be determined at any point during the adjustment procedure.

The adjustment process was performed with the patient in a seated position and included placement of topical anesthetic in the eye, muscle balance testing, placement of eyelid speculum, advancement or recession of an extraocular muscle, removal of mucus from the conjunctival sac, and tying of the muscle suture. All steps of the adjustment process were noted on the blood pressure and rhythm strips along with any record of patient symptoms.

The control group consisted of a group of patients undergoing strabismus correction from July to November 1988. Patients were excluded from study only if the monitoring equipment was unavailable. Patients were studied three to four hours postoperatively by using techniques similar to those described previously for study patients. Control patients were, however, monitored in a supine rather than a seated position, as was done in study patients. There was no ocular manipulation.

All results and information were submitted to one of us (C.C.E.) for analysis, who knew which patients were study or control. Vagal response was defined as a 10% decrease in pulse rate below baseline or a 35-mm Hg decrease in systolic blood pressure below baseline. The vagal response was further defined as chronotropic, vasodepressor, or combined mechanism. The maneuver precipitating the vagal response was identified, and any electrocardiographic abnormality or patient symptom was noted.

Results were analyzed using chi-square analysis and the Wilcoxon rank sums test.

Results

The demographics of the study and control groups were similar. The study group consisted of nine males and 11 females with an age range from 13 to 86 years (average age, 38.2 years). The control group consisted of five males and five females with an age range from 16 to 59 years (average age, 38.4 years). The one difference between the control and study groups was that three patients in the study group had heart disease for which they were being treated.

In the study group, the muscle on adjustable suture varied with the patient diagnosis. Distribution of the muscle on adjustable suture was as follows: medial rectus muscle, 11 patients; lateral rectus muscle, eight patients; inferior rectus muscle, three patients; and superior rectus muscle, three patients. Five of the 20 patients in the study group had two muscles on adjustable suture, for a total of 25 muscles on adjustable suture in the study group.

Thirteen of 65 study patients (65%), compared with two of ten control patients, were noted to have vagal responses. This was highly significant by chi-square analysis ($P < .001$) and Wilcoxon rank sums test ($P < .001$). In the study group, 17 vagal responses were noted in these 13 patients. There were 15 chronotropic responses, one vasodepressor response, and one combined response. Four patients had more than one vagal response during the observation period. Two chronotropic responses were noted in the control group.

No electrocardiographic abnormalities were noted in the control group. One patient with strabismus had a ten-beat run of supraventricular tachycardia. Another patient with strabismus had two separate episodes of ventricular triplets during adjustment.

Only two patients were symptomatic during the adjustment process. One patient became

light-headed, yet never lost consciousness. Another patient became nauseated and vomited.

The event that triggered the vagal response varied among patients. All steps of the adjustment procedure elicited a vagal response in susceptible patients. A vagal response was caused by suture adjustment in 11 patients, a tying procedure in three patients, and placing the speculum in three patients.

Discussion

The oculocardiac reflex is a well-recognized result of ocular stimulation. Although any ocular stimulation can result in the oculocardiac reflex, traction on the extraocular muscles is recognized as most important in eliciting this vagal response. Welhaf and Johnson[3] determined the incidence of the oculocardiac reflex to be 56% in 78 patients with strabismus stimulated with intraoperative traction on the extraocular muscles. Apt, Isenberg, and Gaffney[4] found a 68% response rate in 240 patients undergoing strabismus correction.

The results of our study suggested that the incidence of the oculocardiac reflex when traction is exerted on extraocular muscles during suture adjustment in strabismus correction is similar to the incidence found in the previously mentioned studies. However, results of our study were markedly dissimilar to those of Vrabec, Preslan, and Kushner,[7] who prospectively studied 44 patients undergoing suture adjustment and found an incidence of oculocardiac reflex of only 4.5%. We propose that the discrepancy in incidence between our study and the study by Vrabec, Preslan, and Kushner[7] can be attributed to differences in methodology. We used electrocardiography to monitor heart rate. Vrabec, Preslan, and Kushner[7] used a digital pulse meter, which provides a computer average of heart rate over an eight-second interval with the heart rate monitor. We propose that the digital pulse meter is much less sensitive to bradycardic episodes of short duration compared with electrocardiography. Whereas electrocardiography provides a second-by-second analysis of heart rate, the digital pulse meter uses a computer program that averages eight-second intervals. This digital pulse meter could have missed or disregarded short bradycardic episodes that would have been identified with electrocardiography. Our incidence figures were similar to those of Apt, Isenberg, and Gaffney[4] and Welhaf and Johnson,[3] which supports this claim.

Other important differences between our study and that of Vrabec, Preslan, and Kushner[7] deserve mention. Vrabec, Preslan, and Kushner[7] made adjustments on the postoperative morning, rather than four to six hours postoperatively as we did. Possibly, a patient's susceptibility to vagal responses is greater in the immediate postoperative period. Two of our control patients demonstrated an unexplained postoperative chronotropic response. Also, we performed the adjustment with the patient in a seated position (rather than supine as in the study by Vrabec, Preslan, and Kushner[7]), which might elicit a vasodepressor response. Finally, we used an eyelid speculum (not used by Vrabec, Preslan, and Kushner[7]), which might trigger an oculocardiac reflex. This variance in methods, therefore, prevents accurate comparison of the two studies and might account, to a certain degree, for the increased incidence of oculocardiac reflexes in our study.

Although the definition of the chronotropic vagal response (a 10% decrease in heart rate) was similar to the definition of oculocardiac reflex used in other studies, this definition may be too conservative. Two of our control patients demonstrated a chronotropic vagal response, one of whom had a decrease in heart rate of 32 beats per minute from baseline. Possibly, what is considered "normal" in the immediate postoperative period requires redefinition.

Although we suspect that most vagal responses represent a true oculocardiac reflex, anxiety-related vasovagal responses are also probably included. Despite proper counseling, many patients are apprehensive and fearful of strabismus correction. The stress and anxiety of the adjustment maneuver merely compound the problem. Although any type of ocular stimulation can induce the oculocardiac reflex, it is doubtful that eyelid speculum placement or tying of the muscle sutures represents enough stimulation to result in the oculocardiac reflex. In the six patients in our study in whom these steps resulted in a vagal response, we suspect the vagal response to have been anxiety related. Unfortunately, the available data prevent accurate differentiation between oculocardiac reflex and vasovagal responses. Vrabec, Preslan, and Kushner[7] described a similar experience. One patient had a bradycardic response with cover testing, but no response when traction was exerted on the extraocular muscles. We suspect, as do Apt and Isenberg,[8] that this response was also vasovagal.

Although vagal responses occur commonly during suture adjustment, patients rarely become symptomatic.[6] In a survey of the American Association of Pediatric Ophthalmology and Strabismus membership,[9] the incidence of symptomatic vasovagal reflexes occurring during suture adjustment was 0.28%. In our study, only one patient was symptomatic but recovered quickly before losing consciousness. In this instance, a chronotropic oculocardiac reflex resulted in a decrease in heart rate from 110 to 80 beats per minute (27% below baseline). The patient was placed in the supine position with prompt resolution of symptoms and return of heart rate to normal range.

We suggest that vagal responses are common; however, most patients (65%) will be asymptomatic and symptoms will be unrecognized unless cardiac monitoring is used. The wide disparity in incidence between symptomatic and asymptomatic vagal events can be explained. We suspect that the duration of the bradycardic or hypotensive event determines whether a patient becomes symptomatic. Oculocardiac reflexes of short duration do not result in a marked decrease in cerebral perfusion; therefore, the patient remains asymptomatic. Conversely, if the oculocardiac reflex is of long duration, cerebral perfusion becomes compromised, and the patient becomes light-headed and syncopal. Unfortunately, the duration of the oculocardiac reflexes was not calculated, and therefore, the critical time period for patients experiencing oculocardiac reflexes to become symptomatic is undetermined by this study.

Fortunately, the oculocardiac reflex encountered during suture adjustment is generally a brief, self-limited event, rarely resulting in symptoms or any other sequelae. When oculocardiac reflexes do occur, however, these episodes are disturbing to both patient and physician. Therefore, the physician who performs the adjustment should properly inform patients of this possibility.

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Recession of Both Horizontal Recti Muscles in Duane's Retraction Syndrome With Elevation and Depression of the Adducted Eye

Gunter K. von Noorden, M.D.

Upshoot and downshoot of the adducted eye in Duane's retraction syndrome is thought to be caused by a bridle effect of the co-contracting horizontal recti muscles. A recession of both of these muscles transposes their insertions posteriorly in relation to the center of rotation of the globe, which reduces the bridle effect and decreases the upshoot and downshoot. An 11-year-old girl had Duane's retraction syndrome type III and upshoot and downshoot of the left eye. The left lateral rectus muscle was recessed 8 mm and the left medial rectus muscle 6 mm. At last examination 10½ months postoperatively, the upshoot and downshoot on attempted adduction was no longer present.

THE MECHANISM of elevation and depression of the adducted eye in Duane's retraction syndrome has undergone much clarification in recent years. This phenomenon is thought to be caused by a vertical bridle effect of the co-contracting horizontal recti muscles[1-4] or by a paradoxical co-contraction of the cyclovertical muscles in combination with co-contraction of the horizontal recti muscles.[5-7] The concept of a bridle effect has been confirmed by data obtained in normal subjects with modern imaging techniques, which show that there is little, if any, vertical movement of the horizontal recti muscles in relationship to the orbital walls as the eye is elevated or depressed.[8,9] For the muscle plane to stabilize, the globe must slip beneath the muscles when the eye elevates or depresses. Because of this movement of the globe, the muscle planes of the horizontal recti muscles change their position in reference to the center of rotation. This adds a vertical function to the horizontal action of these muscles during their paradoxical co-contraction on adduction and causes upshoot and downshoot of the eye.

Previously, we have shown that retroequatorial posterior fixation of both horizontal recti muscles reduced this vertical effect in five patients.[4] However, severe mechanical restrictions of horizontal ocular motility may exist in Duane's syndrome, especially in the type III. Such restrictions may limit the surgeon's ability to suture the muscles retroequatorially. In this situation, I found recession of both horizontal recti muscles[1-3] to be equally effective and have used this approach with good results.

Case Report

A 5-year-old girl was not able to move her left eye at initial examination. Her uncorrected visual acuity was 20/20 in each eye and her refractive error was insignificant. She preferred her right eye for fixation. A face turn to the right, estimated to be about 10 degrees, was noted. When the head was passively straightened and in primary position, she had an exotropia of 5 prism diopters at 33-cm fixation distance and of 16 prism diopters at 6-m fixation distance. In right gaze, the exotropia increased to 50 prism diopters and in left gaze an esotropia of 25 prism diopters was present. In the left eye, adduction was markedly limited and abduction was moderately limited, with retraction of the globe and narrowing of the palpebral fissure on attempted adduction and widening of the palpebral fissure on abduction. Upshoot and downshoot of the left eye was noted on

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From the Cullen Eye Institute, Baylor College of Medicine, and the Department of Ophthalmology, Texas Children's Hospital, Houston, Texas.

Reprint requests to Gunter K. von Noorden, M.D., Department of Ophthalmology, Texas Children's Hospital, Houston, TX 77030.

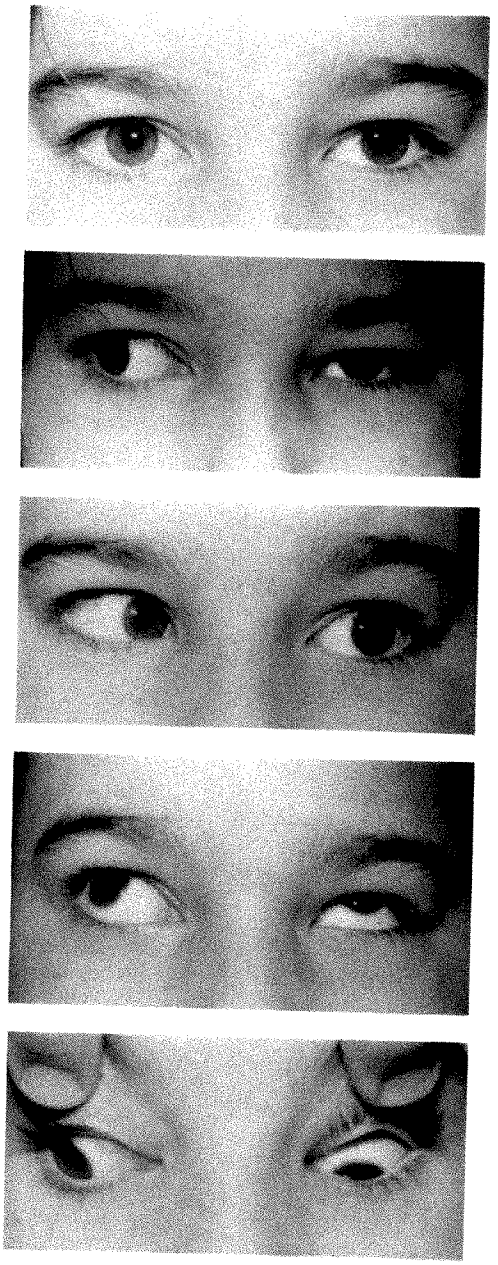


Fig. 1 (von Noorden). Preoperative ductions and versions in Duane's retraction syndrome type III with severe limitation of adduction, narrowing of eyelid fissure on attempted adduction, and moderate limitation of abduction. Note upshoot and downshoot of the left eye on attempted adduction when it was slightly elevated or depressed (bridle effect), but not when it adducted from primary position.

attempted adduction when the eye was slightly elevated or depressed from the primary position (Fig. 1). The remaining results of the eye examination were normal. Duane's retraction syndrome type III of the left eye was diagnosed, and the patient was followed up at irregular intervals without treatment until she was 11 years old. At that time, an examination showed the same findings as were recorded on the first visit, except that she had developed variable exotropia of up to 12 prism diopters at near fixation. Her head turn was unchanged.

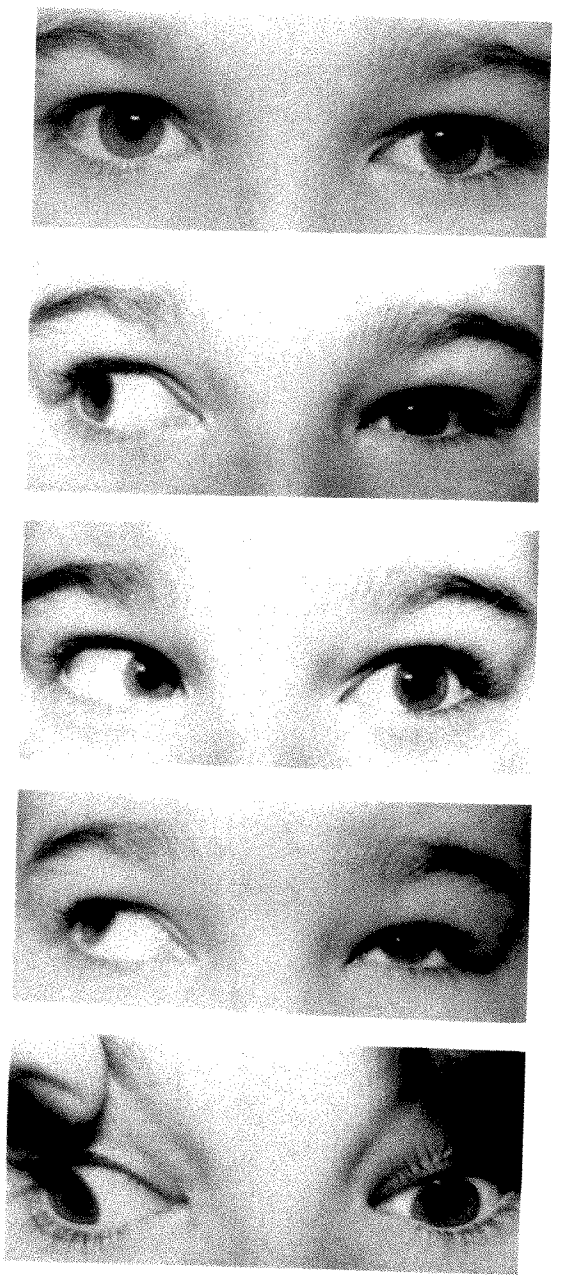


Fig. 2 (von Noorden). Postoperative ductions and versions after recession of both horizontal recti muscles. Upshoot and downshoot are no longer present.

The patient had become embarrassed about

the upshoot and downshoot and her parents requested surgical correction. A posterior fixation of the left medial and lateral recti muscles was scheduled. However, a forced-duction test performed with the patient under general anesthesia showed severe restriction on attempts to move the left eye into adduction and abduction. Because a posterior fixation was technically impossible to perform under these conditions, we recessed the left lateral rectus muscle 8 mm and recessed the left medial rectus muscle 6 mm. More surgical correction was performed on the lateral than on the medial rectus muscle to counteract the small exotropia in the primary position that caused the head turn. The postoperative course was uncomplicated. The head turn was diminished and the upshoot and downshoot of the left eye on attempted adduction was no longer present (Fig. 2). The improvement persisted at last examination, 10½ months postoperatively.

Discussion

Recession of both horizontal recti muscles is a viable alternative to retroequatorial scleral fixation in controlling cosmetically unacceptable elevation and depression of the adducted eye in Duane's retraction syndrome. Because of the ease with which this procedure is performed compared with posterior fixation and its equal effectiveness in controlling the upshoot and downshoot, we no longer use posterior fixation of the horizontal recti muscles in this condition. Both operations work similarly by transposing the effective insertion of the muscles posteriorly in relation to the center of rotation and thus reducing the vertical bridle effect when these muscles co-contract paradoxically in adduction.

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Stereopsis After Congenital Monocular Cataract Extraction

Fred M. Gregg, M.D., and Marshall M. Parks, M.D.

Congenital monocular cataract extraction was performed on a 1-day-old baby girl and a hydrophilic contact lens was fitted. A progressive regimen of part-time occlusive therapy was then instituted. Eight years later, the girl has a visual acuity of 20/25 in the operated-on eye and 50 seconds of arc of stereoacuity that has been confirmed by an independent pediatric ophthalmologist. This patient demonstrates the potential for high-grade stereopsis in congenital monocular aphakia.

THOUGH ONCE CONSIDERED a hopeless situation, successful treatment of congenital monocular cataracts is now well-documented.[1-7] Most studies stress the need for an early surgical procedure, immediate optical correction, and aggressive occlusive therapy of the unaffected eye. Even in patients with excellent binocular vision, however, stereopsis has yet to be reported. Whether this is because of the timing of the surgical procedure, asymmetric inputs, or lack of binocular viewing time is unknown. We studied the visual development and the important aspects of treatment in a unique case of congenital monocular cataract in a newborn infant, who eight years later has excellent stereopsis.

Case Report

A newborn baby girl was noted by her pediatrician to have leukocoria of the left eye. Ophthalmic examination six hours later confirmed the presence of a dense axial cataract with absence of a red reflex. Examination of each dilated eye disclosed no other abnormalities. Bilateral patching was immediately instituted and the parents and pediatrician were consulted. The patient was the child of a gravida 1, para 1, abortus 0 woman. She had been a 3,580-g product of a 40-week uncomplicated pregnancy, labor, and delivery. Her family history was noncontributory for genetic or ocular problems. The girl was normal in every other respect and results of metabolic urine screens were normal.

Approximately 24 hours after birth, the infant was taken to the operating room for examination performed with the infant under anesthesia. The intraocular pressure was 15 mm Hg bilaterally by applanation. The corneal diameters were 10 mm and axial lengths were 17.5 mm in each eye. Keratometry of the affected left eye was 44.00 diopters sphere. Slit-lamp biomicroscopy disclosed a dense axial cataract of the left eye that occupied the regions within and slightly beyond the Y sutures. The opacity was noted to occupy approximately two thirds of the dilated pupillary aperture. Results of indirect ophthalmoscopy around the clear rim were normal. No abnormalities were noted in the right eye.

The patient was immediately prepared for lensectomy by vitreous suction cutter, primary posterior capsulotomy, and anterior vitrectomy. The procedure used closely paralleled that described by Parks.[8] An iridectomy was not performed.

At the conclusion of the surgical procedures, a hydrophilic lens with power +32.50, base curve 7.8, and a diameter of 13.7 mm was fitted. Streak retinoscopy showed a crisp reflex and a 2- to 3-diopter overcorrection for near vision. Both eyes were again patched until the next morning. The next 48 hours consisted of full-time occlusion over the unaffected right eye. A progressive patching schedule was then instituted, which consisted of one hour per day per month of age (Figure). This regimen of patching was chosen empirically in an attempt to permit binocularity in addition to functional vision of the affected eye. When a magnitude of eight hours per day was reached, it was maintained until the patient was 2 years old. During the

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From the Department of Ophthalmology, University of Tennessee, Chattanooga, Tennessee (Dr. Gregg); and Children's Hospital, National Medical Center, Washington, D.C. (Dr. Parks).

Reprint requests to Fred M. Gregg, M.D., 725 Glenwood Dr., Ste. East-782, Chattanooga, TN 37404.

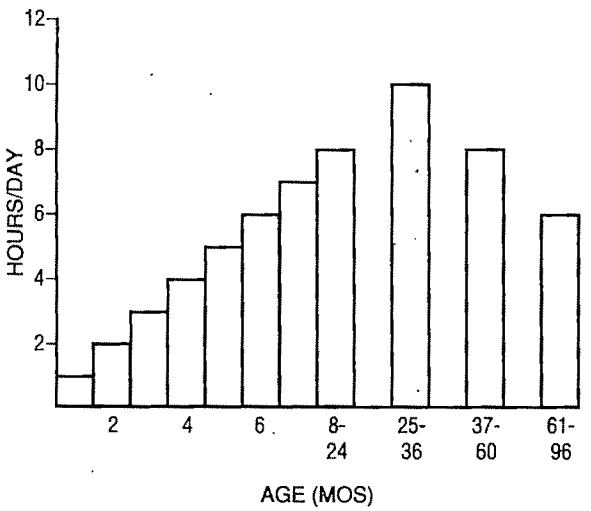


Figure (Gregg and Parks). Waking hours of patching relative to age.

subsequent year, patching was intermittently increased to ten hours per day, but rarely exceeded 75% to 80% of the waking day. At 3 years of age, it was reduced to eight hours after demonstrating 20/40 visual acuity by picture cards and continued straight alignment. At 5 years of age, patching was decreased further to six hours per day. Frequent refractions were performed and lens power was adjusted to correct for 12 to 18 inches. Contact-lens compliance was excellent with removal only once a week for cleaning. At 6 years of age, a rigid gas-permeable lens was substituted because of the development of corneal neovascularization, which subsequently regressed.

In July 1991, eight years postoperatively, she was again examined. Snellen visual acuity measured R.E.: 20/20 and L.E.: 20/25−2 with Jaeger 1 and Jaeger 2, respectively, at near. Motility testing showed orthophoria at distance and near. Fusional responses were elicited from the Worth four-dot test also at distance and near. Stereoacuity of 50 seconds of arc was demonstrated by the Titmus test, and later duplicated by the Randot test. These findings were confirmed by an independent pediatric ophthalmologist (Zane Pollard, M.D., Atlanta, Georgia).

Discussion

The prognosis with congenital monocular cataracts has been disappointing. Although often associated with other anomalies, the principal reason is apparently irreversible amblyopia from lack of form vision in the affected eye.[9]

In 1960, Scheie[10] reintroduced the technique of aspiration for congenital cataracts. Although initial results were discouraging, in 1967 Parks and Hiles[11] suggested that early surgical procedures followed by optical correction and patching could possibly result in better vision.

Apparently, the first successful results were achieved in 1973 by Frey, Friendly, and Wyatt.[1] Their study included three patients with final visual acuities of 20/40 or better. Subsequent studies by Pratt-Johnson and Tillson,[2] Beller and Hoyt,[3] Birch and Stager,[4] Drummond, Scott, and Keech,[5] Pratt-Johnson and Tillson,[6] and Cheng and associates[7] confirmed the potential for excellent vision with congenital monocular cataracts. However, no patient had stereopsis. In the studies by Beller and Hoyt,[3] as well as the later article by Pratt-Johnson and Tillson,[6] this point was specifically addressed. Although some patients had simultaneous perception, it was not accompanied by actual fusion or stereopsis. Additionally, in the study by Cheng and associates,[7] postoperative strabismus was found in all five patients who had 20/40 or better visual acuity, which indicated lack of fusion. In these previous studies, aggressive occlusion of the unaffected eye was emphasized.

We questioned what prevents the occurrence of single binocular vision in a patient with excellent vision in either eye. The seemingly obvious possibilities would be anisometropia/aniseikonia, surgical procedures performed past a critical time, or simple lack of binocular viewing.

Single binocular vision in infants is believed to develop in the first two to three years of life.[12] It depends on a competitive interaction, or synergy, resulting from the inputs of each eye at the cortical level. Visual information originating in the retinal ganglion cells synapses in monocularly segregated laminae of the lateral geniculate nucleus. Postsynaptic geniculocalcarine neurons then project to the level IVc of the visual cortex. Because of the decussative arrangement of the visual pathways in the chiasm, corresponding retinal points from the two eyes eventually arrive at common cortical sites.

Inputs to the visual cortex are normally arranged in alternating stripes called ocular dominance columns, which are monocularly segregated and contain cells with similar receptive fields and orientation.[13] In this respect, they

may be considered the functional unit of the visual cortex, because it is here that integration of visual space occurs. These columns are not present at birth, but develop from competition at the cellular level between activity originating in each eye.[14] Although genetically determined, the columns develop postnatally only in response to activity-dependent modification at the synapse as part of the overall process Flynn[15] called "synaptogenesis." Effective connections are retained and ineffective connections are lost as predicted by Hebb's rule.[16] This process of axonal segregation occurs early in life and probably defines the critical period of visual development, which is thought to comprise the first 17 weeks in humans.[5,7]

Wiesel and Hubel[17] demonstrated that 80% of the cells within the striate cortex of a cat can be independently driven from either eye. These binocularly driven cells have two separate, but nearly identical receptive fields. When the two competing receptive fields of a single neuron are simultaneously stimulated, the binocular feature is enhanced and preserved. However, any factor that prevents competitive synergy, such as suturing of one eyelid, alternating occlusion, or a unilateral media opacity, will cause a marked shift in ocular dominance toward one eye and a permanent reduction in the population of binocularly driven cells.[18] This shift in ocular dominance and reduction in cells is reflected histologically by a marked asymmetry in size of the ocular dominance columns representing the two eyes.[14,19]

Bilateral suspension of formed vision for brief periods of time shows no such rearrangement.[17] This forms the basis of our attempt to place the newborn back in utero visually by binocular occlusion preoperatively.

In our patient, both good monocular visual acuity in the affected eye, and high-grade binocular stereopsis were achieved. We believe the method of occlusion that followed early surgical procedures with immediate optical correction explains the good visual results. Only by allowing the child long periods of binocular viewing, especially in the first few months, was the potential for developing binocular cells possible. Some would argue that only full-time occlusion could overcome the competitive disadvantage of a monocular aphakic eye and enable good vision in that eye. The result in our patient would tend to disprove that as well as the prohibitive effect refractive asymmetry might present. In a study conducted by O'Dell and associates,[20] newborn rhesus monkeys were rendered monocularly aphakic surgically. Without any occlusion of the fellow eye, monkeys with near-point contact-lens correction showed surprisingly good vision.

Part-time occlusion appears to be effective in monocular visual rehabilitation, while possibly allowing binocular interaction to occur. Part-time occlusion also avoids the unfortunate occurrence of occlusive amblyopia, which has been described.[21]

We have recently learned of three other patients operated on at an early age for congenital monocular cataract (optically corrected), who underwent part-time patching and who now have gross stereopsis (Kenneth Wright, M.D., Los Angeles, California, personal communication, February 1992). On the basis of these data and ours, we believe not only is stereopsis a possibility after congenital monocular cataract extraction, but also should be our goal as clinicians.

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OPHTHALMIC MINIATURE

This man seemed one of the most admirable I had ever met. One strange detail: his eyes, which were rather far apart, had an almost ninety-degree range of vision. This ability—I was later able to verify it—was backed by eyesight even better than Ned Land's. When this man fixed his look upon some object, he would frown and squint in such a way as to limit his range of vision; and then he would look. And what a look! How he could magnify objects made smaller by distance! How he could penetrate to your very soul! How he could pierce the surface of the water, so impenetrable to our eyes, and read the ocean depths! . . .

Jules Verne, *20,000 Leagues Under the Sea*
New York, Bantam Books, 1962, p. 56–57

Contralateral Occipital Depression Related to Obstetric Forceps Injury to the Eye

Marguerite B. McDonald, M.D., and Stuart K. Burgess, M.D.

Obstetric forceps pressure strong enough to leave a periorbital depression and corneal injury would probably be severe enough to leave an occipital depression from the opposite forceps blade. The presence of a depression at the correct occipital position would support the diagnosis of forceps injury when the birth history is unknown and the cornea has decompensated enough to make observation of the Descemet's membrane scrolls difficult. We studied six patients with known or suspected obstetric forceps injury to the cornea. Complete ocular examinations included examination for periorbital forceps depressions and posterior skull depressions 180 degrees from the affected cornea (which correlates with the opposite blade of the forceps). All of the patients with Descemet's scrolls had posterior skull depressions. This method of palpation for a contralateral skull depression may assist in the diagnosis of forceps-induced corneal decompensation.

CORNEAL INJURY related to the use of obstetric forceps was first documented in 1898.[1] This injury develops in two distinct phases. First, the traumatized cornea appears cloudy at birth, but clears within a period of weeks. At that time, vertically oriented tears in Descemet's membrane become apparent. These tears or scrolls are permanent and appear as endothelial fissures on scanning electron microscopy.[2] These patients often have myopia, with-the-rule astigmatism, and amblyopia in the affected eye.[3]

The second phase occurs after several decades,[4] when these patients may develop acute corneal decompensation with corneal edema and bullous keratopathy. Previous findings that correlate with forceps injury include the vertical tears in Descemet's membrane and periorbital forceps depressions.[1,5]

We believe that pressure strong enough to cause periorbital depressions would also cause a depression from the opposite blade of the forceps. We examined patients with suspected forceps injuries for an occipital depression on the side of the head contralateral to the affected eye.

Patients and Methods

Four patients with a history of or suspected forceps trauma were examined at the LSU Eye Center or Charity Hospital. Additionally, charts from two previously examined patients were reviewed.

All of the patients were male. Ages ranged from 3 to 66 years with an average age of 41 years. Examinations varied according to patient condition and age. Testing included (when possible) visual acuity, manifest refraction, brightness acuity testing, Lotmar potential acuity testing, slit-lamp examination, specular microscopy with endothelial cell counts, as well as examination for periorbital and occipital forceps depressions. Information concerning birth position was unavailable.

Case Reports

Case 1

A 54-year-old man had a history of forceps injury leading to poor vision in the right eye

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From the LSU Eye Center, Louisiana State University Medical Center School of Medicine, New Orleans, Louisiana. This study was supported in part by United States Public Health Service grant EY02377 from the National Eye Institute (Dr. Kaufman).

Reprint requests to Marguerite B. McDonald, M.D., LSU Eye Center, 2020 Gravier St., Ste. B, New Orleans, LA 70112.

during childhood. Manifest refraction was R.E.: −2.50 +7.00 × 100 and L.E.: +3.75 spherical. Best-corrected visual acuity was R.E.: 20/25− and L.E.: 20/20. Brightness acuity testing yielded 20/30−2 acuity in his right eye and 20/20−1 acuity in his left eye. Lotmar testing demonstrated a potential of 20/40 in the right eye and 20/20 in the left eye. Slit-lamp examination disclosed several small vertical linear tears in Descemet's membrane in his right eye. Endothelial cell counts were 2,300/mm^2 in his right eye and 2,500/mm^2 in his left eye. A right periorbital forceps depression and a left occipital depression in the shape of forceps were noted (Fig. 1).

Case 2

A 3-year-old boy had a history of forceps damage to the left eye. Visual acuity without correction by Allen cards was L.E.: 3/30 and R.E.: 20/30. Retinoscopy disclosed a refractive error of −9.50 +9.00 × 75 in his left eye; his right eye was plano. Slit-lamp examination disclosed vertical tears in Descemet's membrane in the left eye, but no periorbital depression was noted. A right occipital depression in the shape of forceps was observed.



Fig. 1 (McDonald and Burgess). Case 1. A left occipital depression (arrow) in the shape of forceps is visible.

Case 3

A 45-year-old man had been adopted at birth and had no knowledge of obstetric trauma. He had complained of poor vision in his left eye since childhood, and had corneal edema in his left eye at initial examination. Uncorrected visual acuity was L.E.: 20/400 and R.E.: 20/16−3. Manifest refraction was not documented. Slit-lamp examination disclosed horizontal, oblique, and vertical tears in Descemet's membrane in the left eye. The patient underwent penetrating keratoplasty secondary to corneal decompensation. A left periorbital forceps depression (Fig. 2) and a right occipital depression in the shape of forceps were also noted.

Case 4

A 24-year-old man had a history of forceps delivery with poor visual acuity and a history of amblyopia in his right eye. Manifest refraction was R.E.: −8.00 +5.75 × 105 and L.E.: −4.75 +1.25 × 90. Best-corrected visual acuity was R.E.: 20/70 and L.E.: 20/20+2. Brightness acuity testing demonstrated acuities of 20/100 in the right eye and 20/20− in the left eye. Lotmar potential acuity was 20/30 in the right eye and 20/20 in the left eye. Slit-lamp examination disclosed horizontal and vertical tears in Descemet's membrane in the right eye. Endothelial



Fig. 2 (McDonald and Burgess). Case 3. A marked left periorbital depression (arrow) is visible.

cell counts were 1,300/mm^2 in the right eye and 2,500/mm^2 in the left eye. No periorbital depression was seen, but a left occipital depression in the shape of forceps was noted.

Case 5

A 66-year-old man had a history of a difficult delivery, but it was not possible to determine whether forceps had been used. At initial examination, the patient had a three-year history of corneal decompensation in the right eye. Manifest refraction was R.E.: +1.75 spherical and L.E.: +2.25 +0.50 × 45. Best-corrected visual acuity was R.E.: 20/60 and L.E.: 20/20−1. Slit-lamp examination disclosed vertical tears in Descemet's membrane and corneal edema in the right eye. Old pigmented keratic precipitates and a low-grade inflammation were also noted in the anterior chamber of the right eye. Brightness acuity testing yielded an acuity of 20/300 in the right eye and was not performed on the left eye. Lotmar testing was not performed. The decompensating cornea was replaced by penetrating keratoplasty. No periorbital depression was seen, but a left occipital depression in the shape of forceps was noted.

Case 6

A 52-year-old man had an unknown birth history and complained of poor vision in his right eye since childhood. Manifest refraction of +4.25 +3.75 × 80 disclosed a visual acuity of 20/70, with a brightness acuity of 20/400, in his right eye. Manifest refraction was +0.25 spherical, with a brightness acuity of 20/20, in his left eye. Lotmar testing demonstrated a potential acuity of 20/40 in his right eye and 20/20 in his left eye. Slit-lamp examination disclosed vertical tears in Descemet's membrane in the right eye (Fig. 3). Endothelial cell counts were 900/mm^2 in his right eye and 2,200/mm^2 in his left eye. No periorbital depression was seen, but a left occipital depression in the shape of forceps was noted.

Results

All six patients had vertical tears in Descemet's membrane and were considered to have corneal forceps injuries. All had occipital depressions in the expected position. Two had periorbital forceps depressions. Four of the six had injuries to the right eye. Five of the six patients were anisometropic. Manifest refraction was not available in one of the patients (Case 3). Three of the six patients were myopic, and two of the six were hyperopic.

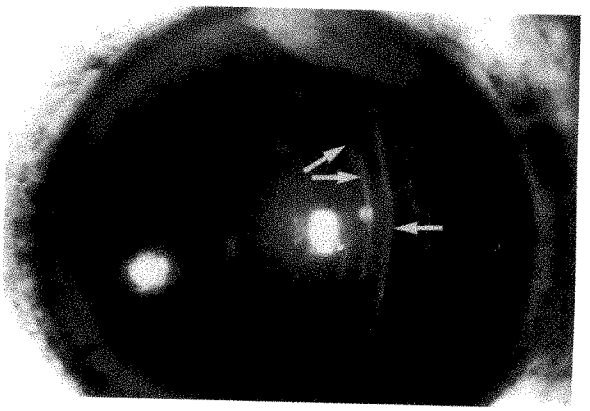


Fig. 3 (McDonald and Burgess). Case 6. Slit-lamp biomicroscopy shows marked vertical tears (arrows) in Descemet's membrane in the right eye.

Four of five patients with known refractions had astigmatism, which ranged from +3.75 to +9.00 diopters, with axes from 75 degrees to 100 degrees. Brightness acuity testing in four cases showed decreases in visual acuity from one to five lines. Lotmar testing of four patients showed potential visual acuity in the traumatized eye within three Snellen lines of the opposite eye in each case.

Specular microscopy performed on three patients disclosed that traumatized eyes showed decreases in the density of endothelial cells ranging from 200 to 1,300 cells per mm^2, when compared to unaffected eyes. However, the extent of the decrease varied considerably, and statistical analysis was unreliable because of the small number of cases. At initial examination, two of the six patients had corneal decompensation that required penetrating keratoplasty.

Discussion

Obstetric forceps–inflicted trauma to the cornea can often be difficult to diagnose in adults. These patients may have Descemet's tears or corneal decompensation, or both. At initial examination, they may be unaware of birth trauma or the use of forceps during their delivery. Additionally, birth records are often unavailable.

The differential diagnosis for the vertical scrolls in Descemet's membrane is small and

includes only forceps injury and syphilitic interstitial keratitis. The less-experienced observer may include posterior polymorphous dystrophy and congenital glaucoma in the differential diagnosis. Although a periorbital forceps depression is a well-known associated finding that facilitates diagnosis, it is not present in every case and was present in only one third of the cases in our series. One of us (M.B.M., unpublished data, 1980) previously noted a depression on the contralateral occiput 180 degrees from the traumatized cornea on a patient with forceps injury to the eye. Since that time, most patients who have this history at initial examination have been examined for this finding, and it has been present to varying degrees in all of those patients.

These occipital depressions vary in size and are difficult to palpate in some patients. They are also more easily detected by comparing both sides of the skull at the same time. The occipital depression can be palpated through the patient's hair.

We believe that this depression is caused by pressure from the forceps blade opposite the one that inflicted the ocular damage. All six of the patients in this series who had corneal damage from obstetric forceps also had a contralateral occipital depression.

Four of six of the patients had forceps injuries to the right eye. Previous studies have shown a preponderance of injuries to the left eye, which has been attributed to the high frequency of left occipitoanterior presentation of the head during delivery.[6] Although most patients may be affected in the left eye, our series shows that the right eye is also often affected. Additionally, although most patients develop myopic astigmatism, two of six of our patients were hyperopic, and one of six had no astigmatism. One patient (Case 3) did not have a documented manifest refraction.

Specular microscopy of three patients indicated that traumatized eyes have fewer endothelial cells than unaffected eyes, as would be expected by the presence of tears in Descemet's membrane in the traumatized eyes. However, the difference in number of endothelial cells between traumatized and unaffected eyes in this small study varied considerably, from 200 to 1,300 cells per mm^2.

At initial examination, two of the six patients had corneal decompensation that required penetrating keratoplasty. The actual proportion and characteristics of patients with forceps injuries who develop decompensation would be valuable prognostic information.

We believe that although obstetric forceps injuries to the eye have been well documented for many years, the diagnosis remains difficult. Adults often have sudden monocular corneal decompensation, but it is not always easy to observe the vertical scrolls in Descemet's membrane. Also, patients often have no information concerning their birth, and birth records are often unavailable. We found that palpation of the contralateral occipital region for a forceps depression can be a quick, easy, and valuable method to support the diagnosis of forceps delivery or trauma, or both, and may assist in diagnosis of forceps-induced corneal decompensation.

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Ophthalmic Involvement in Myo-neuro-gastrointestinal Encephalopathy Syndrome

Anisa B. Threlkeld, M.D., Neil R. Miller, M.D., Karl C. Golnik, M.D., John W. Griffin, M.D., Ralph W. Kuncl, M.D., Donald R. Johns, M.D., Mohamed Lehar, M.D., and Orest Hurko, M.D.

We studied the clinical, histopathologic, neuroradiologic, biochemical, and genetic profile of a patient with the myo-neuro-gastrointestinal encephalopathy syndrome, a recently described multisystem mitochondriopathy characterized by blepharoptosis and ophthalmoparesis. The patient had severe intestinal pseudo-obstruction and a mixed demyelinating and axonal neuropathy. Abnormal collections of mitochondria in nerve and muscle as well as diffuse white matter disease were present. Cytochrome oxidase activity in muscle mitochondria was reduced. No mitochondrial DNA deletions were detected.

HUMAN MITOCHONDRIOPATHIES are characterized by abnormalities of mitochondrial structure, number, or function and have been recognized in the context of numerous clinical syndromes, many of which have ophthalmic findings.[1,2] These syndromes are usually classified according to clinical manifestations and include apparently isolated myopathies and neuropathies, as well as encephalomyopathies and neuroencephalomyopathies. The most frequent ophthalmic manifestations in these conditions are blepharoptosis and ophthalmoparesis, but retinal pigmentary changes,[3] optic atrophy,[4-6] and homonymous hemianopsia or cerebral blindness secondary to associated strokes[5] also occur. Timely diagnosis is important because potentially devastating multisystem consequences, such as cardiac dysrhythmias, stroke, and intestinal hypomotility are associated. Ophthalmologists are in a unique position to diagnose a mitochondriopathy because of early and frequent ocular involvement. We examined a patient with such a disorder in whom the diagnosis was suggested by examination of the ophthalmic signs.

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From the Wilmer Ophthalmological Institute (Drs. Threlkeld, Miller, and Golnik), and Departments of Neurology (Drs. Griffin, Kuncl, Johns, Lehar, and Hurko), Medicine (Dr. Hurko), and Neuroscience (Dr. Griffin), Johns Hopkins Hospital, Baltimore, Maryland. This study was supported in part by the Jay Slotkin Fund for Neuromuscular Research, Baltimore, Maryland (Dr. Kuncl).

Reprint requests to Neil R. Miller, M.D., Maumenee B-109, Wilmer Ophthalmological Institute, Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21205.

Case Report

A 26-year-old woman with a history of polycystic ovaries developed the acute onset of nausea, vomiting, and lower abdominal pain in 1989. Examination disclosed numerous diverticula in the small intestine and a ruptured jejunal diverticulum. Histopathologic examination of the surgically removed jejunal specimen and appendix showed incomplete longitudinal muscle with ganglion cells located just below the serosa. Myoelectric studies disclosed normal gastric activity, but no propagation of migratory motor complexes, which suggested a failure of motility. The patient developed frequent episodes of nausea and vomiting that necessitated parenteral alimentation. Complications of this therapy included sepsis, pulmonary embolism, and thrombosis of the catheterized veins. Gastrostomy tube feedings failed because of dysmotility, as did an attempt at conversion to jejunostomy. Prokinetic agents, including erythromycin and cisapride, were unsuccessful in improving intestinal motility.

The patient was referred to our institution when her nutritional status continued to deteriorate. A neuro-ophthalmic examination was conducted to evaluate blepharoptosis.

The patient had no ocular complaints and

specifically denied double vision. However, she had been told by an ophthalmologist six months earlier that she had mild blepharoptosis and that her eyes were "not moving well." Visual acuity with correction was R.E.: 20/20 and L.E.: 20/30. Near vision at 16 inches was R.E.: J1 and L.E.: J2. Color vision and pupillary reactions were normal. Visual fields were full to confrontation and there was no red desaturation across the horizontal or vertical midlines. The patient's eyes were orthotropic at distance and near, but the patient had poor ductions and versions in all directions, especially in upgaze (Fig. 1). Saccades were slow and pursuit was slightly saccadic. Trace eyelid swelling and 1-mm blepharoptosis were present bilaterally. There was no proptosis. Facial sensation was normal and symmetric. The orbicularis oculi muscles were weak bilaterally. A Tensilon test resulted in no change in ophthalmoparesis or blepharoptosis. Results of tonometry, slit-lamp examination, and ophthalmoscopy were normal except for mild peripheral pigmentary changes. A mitochondrial abnormality was suspected on the basis of these findings, and a neuromuscular examination was performed.

Neurologic examination disclosed proximal muscle weakness and mild ataxia. Magnetic resonance imaging of the head showed diffuse white matter disease, notably in the periventricular and subcortical areas as well as in the pons. Electrocardiography showed no conduction defects. Serum levels of vitamin E and lactic acid were normal.

Motor nerve conduction velocities in both the median and ulnar nerves were slowed, but evoked motor amplitudes were normal, indicating a demyelinating neuropathy. In the legs, the amplitudes of sensory and motor responses were reduced, and both sensory and motor conduction velocities were slowed, indicating a mixed demyelinating and axonal pattern. Electromyography of the right anterior tibial muscle disclosed clinical signs of chronic partial denervation and reinnervation.

Biopsy of the sural nerve confirmed a demyelinating neuropathy with a mild degree of axonal degeneration. Light and electron microscopy of the sural nerve specimen showed a mild reduction in the number of myelinated fibers (density, 7,310 fibers/mm^2; normal median nerve, 9,400 fibers/mm^2 [range, 7,500 to 11,800]). Circlets of supernumerary Schwann cells grouped together to form small onion bulb-shaped clusters, which surrounded numerous myelinated fibers. Unusual collections of mitochondria within Schwann cells were seen in a few fibers (Fig. 2). These findings indicated a chronic mixed neuropathy with prominent demyelination and remyelination in addition to myelinated fiber loss.

Biopsy of the left quadriceps femoris muscle showed variation in myofiber size, with numerous scattered atrophic fibers and a few degenerating fibers. No ragged red fibers were present. By electron microscopy, most fibers had small myeloid figures and small autophagic profiles, most of which contained distinct mitochondrial remnants or had other features suggesting mitochondrial derivation (Fig. 3). In these regions,

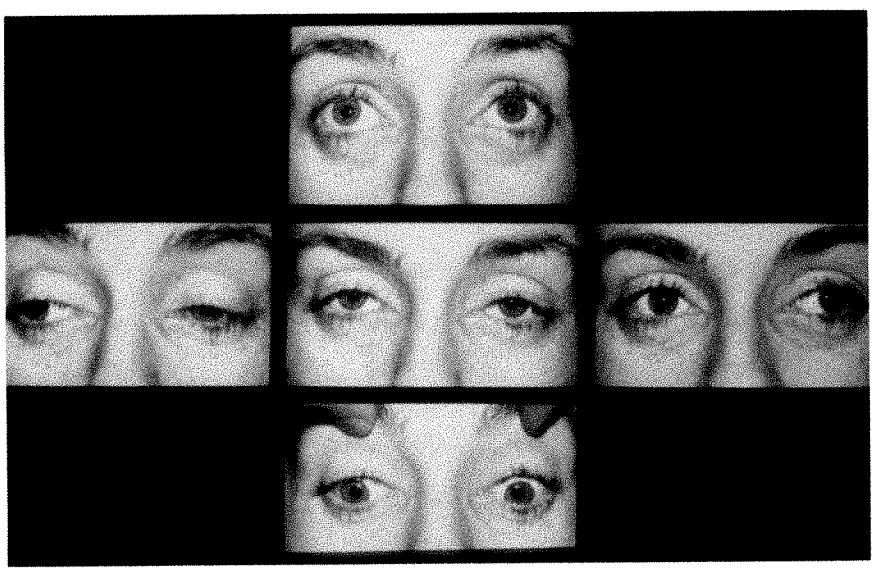


Fig. 1 (Threlkeld and associates). External appearance and ocular motility of patient, demonstrating bilateral, symmetric blepharoptosis, and ophthalmoparesis.

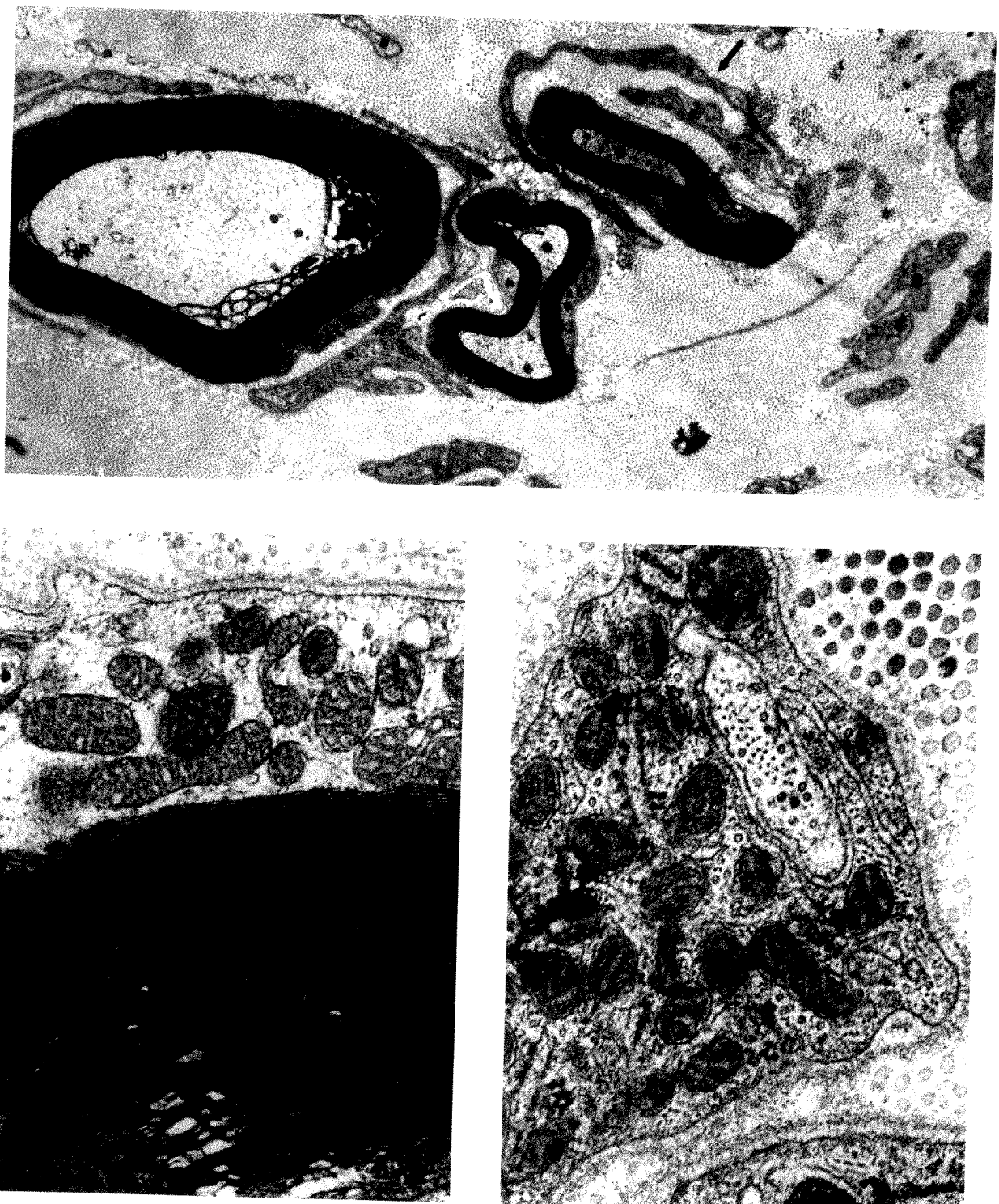


Fig. 2 (Threlkeld and associates). Top, Electron micrograph of a transverse section of sural nerve showing small onion bulb-shaped clusters of Schwann cells (arrow) (×77,000). Bottom left, Prominent accumulation of mitochondria in the abaxonal Schwann cell cytoplasm (×39,000). Bottom right, Schwann cell containing numerous mitochondria (×56,000).



Fig. 3 (Threlkeld and associates). Electron microscopic view of a quadriceps femoris muscle biopsy specimen. Top, Small myeloid figures or autophagic membrane profiles (× 22,800). Bottom, Some myeloid figures and autophagic membrane profiles merge with the outer membrane of mitochondrial remnants (× 18,600).

other mitochondria were often shrunken, swollen, or pleomorphic. There was no excess of mitochondria. No paracrystalline or excessive granular inclusions were present.

Histochemical staining for cytochrome oxidase was absent in some of the muscle fibers that stained darkly with the intramitochondrial enzyme, succinate dehydrogenase, which suggested abnormal mitochondrial function. Unlike in other mitochondrial disorders, these large numbers of mitochondria were present not only in slow-twitch oxidative fibers, but also in fast-twitch oxidative glycolytic fibers (Fig. 4). Biochemical study of freshly isolated skeletal muscle mitochondria disclosed cytochrome oxidase activity to be 21.3% of the mean normal value by polarography.[7]

No mitochondrial DNA deletion was detected by the widely interspaced primer polymerase chain reaction technique,[8] or by Southern blot analysis of linearized mitochondrial DNA using a mitochondrial DNA-specific probe.[9] The mitochondrial transfer RNA (trRNA)-leucine (dihydrouridine) mutation at position 3243, which has been associated with the mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes syndrome, as well as with chronic progressive external ophthalmoplegia, was not detected by an Apa I digest of polymerase chain reaction-amplified mitochondrial DNA.[10]

Discussion

Mitochondrial DNA defects have been implicated in the pathophysiologic characteristics of several syndromes well known to ophthalmologists, including the Kearns-Sayre syndrome[11]; chronic progressive external ophthalmoplegia[12]; Leber's hereditary optic neuropathy[6,13]; the mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes syn-

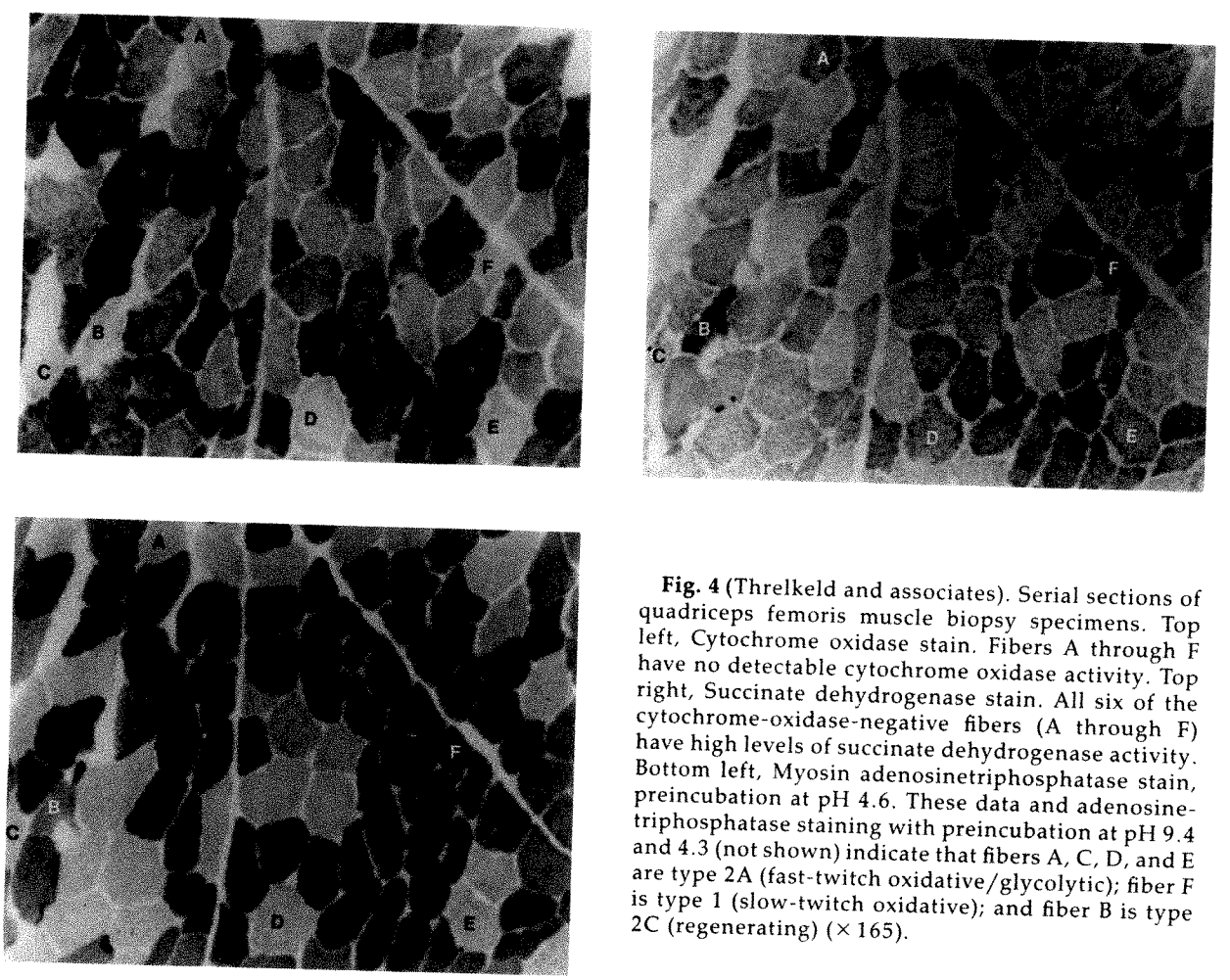


Fig. 4 (Threlkeld and associates). Serial sections of quadriceps femoris muscle biopsy specimens. Top left, Cytochrome oxidase stain. Fibers A through F have no detectable cytochrome oxidase activity. Top right, Succinate dehydrogenase stain. All six of the cytochrome-oxidase-negative fibers (A through F) have high levels of succinate dehydrogenase activity. Bottom left, Myosin adenosinetriphosphatase stain, preincubation at pH 4.6. These data and adenosinetriphosphatase staining with preincubation at pH 9.4 and 4.3 (not shown) indicate that fibers A, C, D, and E are type 2A (fast-twitch oxidative/glycolytic); fiber F is type 1 (slow-twitch oxidative); and fiber B is type 2C (regenerating) (× 165).

drome[14]; and myoclonic epilepsy with ragged red fibers syndrome.[4] The association of gastrointestinal abnormalities with combinations of myopathy, nervous system involvement, and ophthalmic signs has been infrequently described, but is now emerging as a distinct group in the ever-expanding spectrum of mitochondrial multisystem diseases.[15-19]

Our patient had clinical signs and symptoms of a multisystem disorder characterized primarily by gastrointestinal dysfunction, but which included blepharoptosis, external ophthalmoparesis, myopathy, neuropathy, and neuroimaging evidence of encephalopathy. Biopsy of the jejunum showed abnormal gastrointestinal smooth muscle, and results of biochemical analysis of skeletal muscle were consistent with a deficiency in mitochondrial cytochrome oxidase. Bardosi and associates[17] described similar findings in a 42-year-old woman, including external ophthalmoplegia, malabsorption, muscle atrophy, and polyneuropathy. Hypodensities of the cerebral white matter were evident on computed tomography, and ocular and skeletal muscle specimens contained ragged red fibers. Biochemical analysis of liver and muscle tissues showed a partial defect of cytochrome c oxidase. Blake and associates[18] described two patients with similar findings. Abnormalities were not found on analysis of their mitochondrial DNA. Five additional patients with a familial syndrome of polyneuropathy, ophthalmoplegia, leukoencephalopathy, and intestinal pseudo-obstruction were described by Simon and associates.[19] This syndrome is clinically similar to the myo-neuro-gastrointestinal encephalopathy syndrome and may represent the same entity. Our patient's clinical characteristics, biopsy results, and the biochemical defect in cytochrome oxidase activity were consistent with those seen in the patients diagnosed with this disease.[17,18] In our patient, biochemical and histochemical data showing a partial defect in cytochrome oxidase enzyme activity and focal histochemical absence of cytochrome oxidase in some succinate dehydrogenase-positive myofibers provided complementary evidence of altered mitochondrial function that correlated with focal mitochondrial degeneration. There were similar collections of mitochondria within Schwann cells, correlating with the presence of a demyelinating neuropathy.

The molecular basis for this disorder has not yet been identified. No mitochondrial DNA deletion was found, nor was the mitochondrial point mutation known to affect the trRNA of patients with the mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes syndrome and with chronic progressive external ophthalmoplegia,[10] identified in our patient. This entity is possibly autosomal recessive, involving an abnormality of either nuclear or mitochondrial DNA, both of which are necessary for normal mitochondrial function. Such an inheritance pattern is compatible with the history of Bardosi's original patient, who was the product of a consanguineous marriage, and has been described in patients with the similar clinical features of ophthalmoplegia and intestinal pseudo-obstruction (oculogastrointestinal muscular dystrophy).[20] Interestingly, three different mitochondrial trRNA mutations have been found in a patient with chronic intestinal pseudo-obstruction, myopathy, and ophthalmoplegia.[21]

Diagnosis of such a multisystem mitochondriopathy can be difficult because the ophthalmic findings may not be recognized as elements of a generalized neuromuscular disorder, the peripheral polyneuropathy and myopathy may be misinterpreted as complications of the gastrointestinal abnormality, and the encephalopathy present on neuroimaging can be clinically undetected. Therefore, the clinical index of suspicion must be high and we suggest that the diagnosis of a mitochondrial disorder should be considered in all patients with ophthalmoparesis and blepharoptosis and multisystem disease.

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Corneal Endothelial Cytoskeletal Changes in F-Actin With Aging, Diabetes, and After Cytochalasin Exposure

Eung K. Kim, M.D., Dayle H. Geroski, Ph.D., Glenn P. Holley, B.S., Steven I. Urken, B.S., and Henry F. Edelhauser, Ph.D.

We investigated the changes in endothelial cytoskeletal F-actin that occur with aging, diabetes, and exposure to cytochalasin D. Rabbit corneas, human donor corneas (with or without polymegethism), and corneas of diabetic individuals were studied. Endothelial F-actin was stained using nitrobenzoxadiazole-phallacidin. Results of these experiments demonstrated that F-actin of the rabbit and human corneal endothelium was arranged in linear circumferential strands that formed a hexagonal array. After in vitro perfusion of cytochalasin D to the corneal endothelium, the F-actin became randomly distributed throughout the cytoplasm, the hexagonal shape of the endothelial cell was disrupted, and endothelial permeability to carboxyfluorescein increased. Changes in F-actin were also observed in the endothelium of the human corneas with polymegethism, and in donor tissue having had previous posterior chamber intraocular lens implantation. The corneas of diabetic individuals also showed marked irregular F-actin fibers crossing the endothelial cell cytoplasm. These abnormal patterns of F-actin may contribute in part to the polymegethism observed in the corneal endothelial cells and may be the result of constant stress in cell volume regulation, particularly in the corneas of diabetic individuals.

THE NORMAL corneal endothelium is a monolayer of cells with a regular hexagonal pattern. This cell arrangement is the most stable thermodynamically and geometrically for two-dimensional arrays. Since the human corneal endothelium does not proliferate,[1] its ability to compensate for cell loss is limited. If human endothelial cells are damaged, healing occurs by enlargement and migration of the remaining cells to cover the defect. This results in an increase in the cell area.[2]

The functional capacity of the endothelium can be correlated with its structure. Rao and associates[3] indicated that polymegethism is closely correlated with the susceptibility to trauma, and that more postoperative edema developed after cataract extraction in those patients with preoperative polymegethism.

F-actin, a major component of the cellular cytoskeleton, has a key role in maintaining cellular structure. F-actin, assembled through the polymerization of monomeric G-actin,[4] is not a permanent, static structure. G-actin monomers are continually added and lost; thus the cytoskeletal shape of the cell is in dynamic equilibrium and can adapt to environmental stresses. Previous studies by Gordon, Essner, and Rothstein[5] and Gordon[6] demonstrated that normal polygonal endothelial cells are characterized by circumferential bands of F-actin located at the apical portion of cell-cell borders. Fujino and Tanishima[7] studied F-actin changes in rabbit corneal endothelium during wound healing in vivo with the nitrobenzoxadiazole-phallacidin method and showed many fibers throughout the cytoplasm of cells migrating to the wound area. Jumblatt, Matkin, and Neufeld[8] demonstrated that epidermal growth factor or indomethacin, or both, can cause elongation and redistribution of F-actin into a diffuse cytoplasmic pattern in cell-cultured endothelial cells. All of these studies illustrate the importance of F-actin in the cytoskeletal structure of endothelial cells.

We evaluated F-actin changes in normal rabbit and human corneal endothelial cells after cytochalasin treatment (a known inhibitor of

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From the Department of Ophthalmology, Emory University School of Medicine, Atlanta, Georgia. This study was supported by E. W. Anderson Fellowship, in part by National Institutes of Health grants EY00933, EY05609, P30 EY06360 (a departmental core grant), and Research to Prevent Blindness, Inc., New York, New York.

Reprint requests to Henry F. Edelhauser, Ph.D., Department of Ophthalmology, Emory University Eye Center, 1327 Clifton Rd. N.E., Atlanta, GA 30322.

F-actin polymerization) and compared these cytoskeletal changes to those that might develop in the corneal endothelium of diabetic individuals, donor corneas with extreme polymegethism, and human corneas after intraocular surgical procedures.

Material and Methods

Perfusion of the corneal endothelium—Twelve male and female 3-month-old (2.0- to 2.5-kg) and six 26-month-old (5-kg) New Zealand White rabbits were anesthetized with xylazine and ketamine HCl and killed with pentobarbital. All rabbits were used in accordance with the Association for Research in Vision and Ophthalmology Resolution on the Use of Animals in Research. The eyes were enucleated and the corneas were excised and mounted in the in vitro specular microscope for endothelial perfusion as previously described.[9] Eight human donor corneas (Georgia Eye Bank, Atlanta, Georgia) from nondiabetic donors older than 40 years of age and five corneas from diabetic donors were similarly mounted for in vitro perfusion. Rabbit corneas were perfused with glutathione bicarbonate Ringer's solution[10] and human corneas were perfused (37 C) with balanced saline solution (BSS Plus, Alcon Laboratories, Fort Worth, Texas) for a 60-minute equilibration period. The experimental rabbit corneal endothelium of the matched pair was then perfused with cytochalasin D (2 μg/ml) in glutathione bicarbonate Ringer's solution for 40 to 60 minutes while the control corneal endothelium was perfused with glutathione bicarbonate Ringer's solution. The experimental human corneal endothelium was perfused with cytochalasin D (5 μg/ml) in balanced saline solution for 60 minutes. The anterior corneal surface was covered with silicone oil during the perfusion, to minimize evaporation at the anterior corneal surface and to optically couple the microscope objective to the tissue.

Nitrobenzoxadiazole-phallacidin staining of F-actin filament—The cornea with a 2- to 3-mm scleral rim was fixed in 10% neutral formalin for 90 minutes. A corneal button 8 mm in diameter was trephined from the central cornea and the endothelium with Descemet's membrane (including a small portion of posterior stroma) was removed from the overlying stroma with forceps under the dissecting microscope. Eight radial incisions were made in the periphery of the sheet of endothelium and Descemet's membrane to permit a flat preparation of the cornea.[11]

The flat preparations of rabbit and human corneal endothelium were stained with 1.64×10^{-4} mol/l nitrobenzoxadiazole-phallacidin (Molecular Probes, Inc., Eugene, Oregon) for 30 minutes at 37 C for visualization of F-actin filaments. After a buffer (phosphate-buffered saline solution; 0.01 mol/l, pH 7.2) wash, tissues were mounted on a nonfluorescent glass slide in a buffer-glycerol (1:1) mixture and were photographed using a Nikon fluorescence microscope with filter DM 510 (excitation, 450 to 490 nm; barrier, 520 nm).[7,12]

Cytochalasin D permeability studies—The method of Watsky, McDermott, and Edelhauser[13] was used to measure endothelial permeability to carboxyfluorescein. After epithelial debridement, isolated corneas were mounted in the in vitro specular microscope and the endothelium was perfused with glutathione bicarbonate Ringer's solution for a 60-minute stabilization period. The perfusate was then changed to cytochalasin D (2 μg/ml) in glutathione bicarbonate Ringer's solution and the endothelium was perfused for an additional 40 minutes. The anterior surface of the cornea was covered with silicone oil. The oil was removed after ten minutes of cytochalasin D perfusion and 0.3 ml of glutathione bicarbonate Ringer's solution containing 0.26 mmol/l carboxyfluorescein was applied to the corneal surface. The carboxyfluorescein was removed from the corneal surface after 30 seconds. The anterior corneal surface was swabbed and silicone oil was reapplied. The glutathione bicarbonate Ringer's solution perfusate was then collected in a preweighed test tube for 30 minutes. The mass of carboxyfluorescein in the perfusate (M_p) was determined spectrofluorometrically. At the termination of the perfusion, corneas were blotted dry and placed in balanced saline solution for 48 hours for carboxyfluorescein elution. The carboxyfluorescein concentration in the eluate was measured by spectrofluorometry and stromal dye mass (M_s) was calculated. The cornea-aqueous transfer coefficient ($k_{c.ca}$)[13] and endothelial permeability (P_{ac})[14] were calculated as:

$$k_{c.ca} = [\ln(M_p + M_s) - \ln M_s]/t$$
$$P_{ac} = k_{c.ca} \times R_{ca} \times q$$

where t is the time after dye application (30 minutes). The R_{ca} value of 1.07 is the steady-

state distribution ratio used in this study,[13] and q is the average stromal thickness obtained from the three final readings of the perfusion. Statistical significance was determined with a paired *t*-test.

Results

F-actin fibers of the normal endothelium from a 3-month-old rabbit were mainly located adjacent to lateral cell membranes in circumferential bands that formed hexagons. No dense F-actin fibers were seen in the cytoplasm (Fig. 1). The F-actin fibers at the borders between cells were composed of two major bands running parallel along the periphery of the cell. Numerous interconnecting strands joined these two bands. In the normal human endothelium, the F-actin fibers were similarly arranged adjacent to cell membranes, forming a hexagonal pattern (Fig. 2).

When the corneal endothelium of the 3-month-old rabbit was perfused with cytochalasin D (2 μg/ml) for one hour, the cells lost their hexagonal array and separated into irregularly shaped clumps or islands of cells (Fig. 3, left) with breaks in the junctions between these islands. The actin fibers located at the cell border lost their shape and condensed F-actin fibers were found around the nucleus (Fig. 3, left). Scanning electron microscopy (Fig. 3, right) showed cells that were pulled apart in clumps, with areas of thin cytoplasmic membrane covering other areas. The endothelium of 26-month-old rabbits showed changes with cytochalasin D (2 μg/ml, one hour) perfusion that were comparable to those observed in the 3-month-old rabbits. Carboxyfluorescein permeability (mean ± SEM) of the endothelium of four rabbit corneas perfused with cytochalasin D increased significantly to $7.97 \pm 0.69 \times 10^{-4}$ cm/min compared to $3.96 \pm 0.65 \times 10^{-4}$ cm/min for the paired control corneas (significantly different at $P < .01$ with a paired *t*-test).

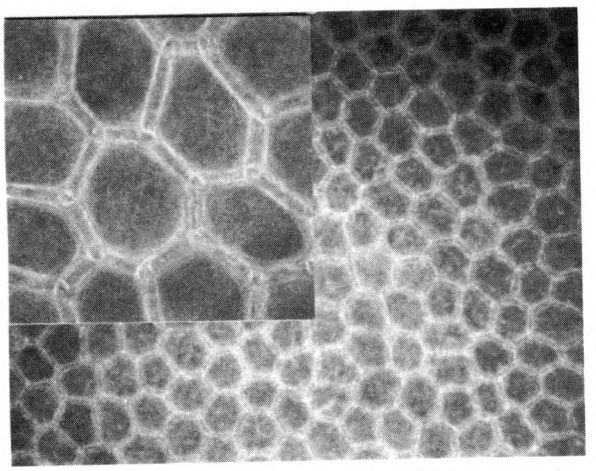


Fig. 1 (Kim and associates). Nitrobenzoxadiazole-phallacidin–stained F-actin fibers of the corneal endothelium of a 3-month-old rabbit. F-actin fibers are mainly located adjacent to cell membranes, forming hexagons (× 250; inset, × 630).

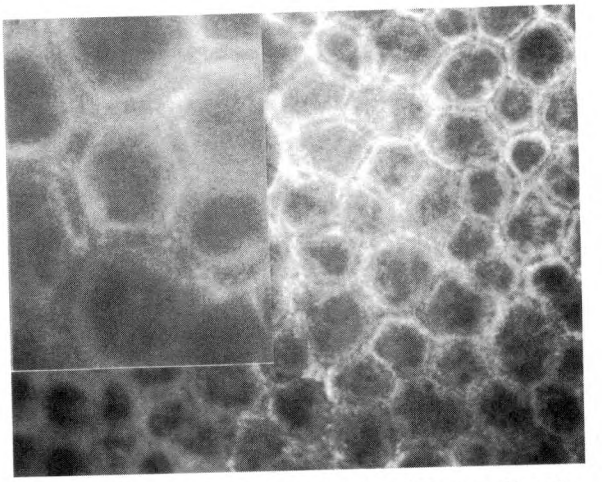


Fig. 2 (Kim and associates). Nitrobenzoxadiazole-phallacidin–stained F-actin fibers of the normal corneal endothelium from a 78-year-old human. F-actin fibers are mainly located adjacent to cell membranes, forming hexagons, although some cells are pentagonal in F-actin shape (× 250; inset, × 630).

Human corneal endothelium, perfused with a 2.5-fold greater concentration of cytochalasin D (5 μg/ml) for one hour, showed slight changes in F-actin with some cytoplasmic staining. These changes, however, were not as marked as those seen in the cytochalasin D–perfused rabbit corneas and the cells retained their hexagonality (Fig. 4, top left). Scanning electron microscopy (Fig. 4, top right) confirmed that the endothelial monolayer remained intact and cell junctions were preserved. However, cytochalasin D caused some irregularity of the anterior endothelial cell surface (Fig. 4, bottom left, transmission electron microscopy).

The endothelium of human corneas with severe polymegethism was characterized by an increased complexity of F-actin along the cytoplasmic membrane (Fig. 5). All of the F-actin fibers, however, were associated with the circumferential cytoskeleton and were not dispersed throughout the cytoplasm.

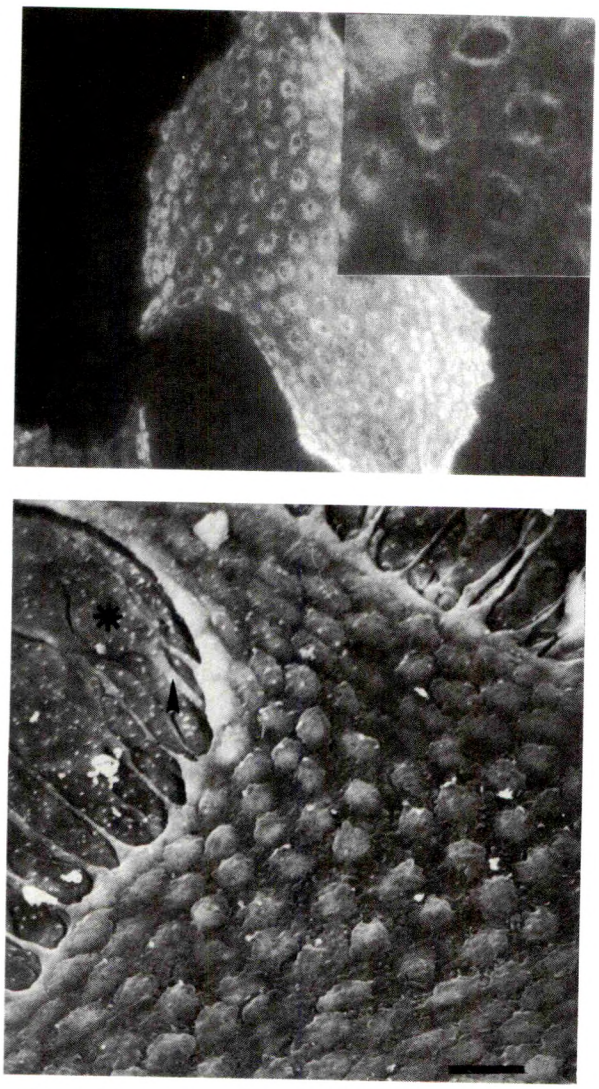


Fig. 3 (Kim and associates). Rabbit corneal endothelium after perfusion with cytochalasin D (2 μg/ml) for one hour. Top, Nitrobenzoxadiazole-phallacidin staining shows that F-actin fibers normally located at the cell border are absent and condensed F-actin fibers around the nucleus are seen. Areas of cells separate and form islands of cells without hexagonal pattern (× 250; inset, × 630). Bottom, Scanning electron microscopy shows areas of cells pulled apart into islands with thin strands of cytoplasmic membrane (arrowhead) remaining attached to Descemet's membrane at the cell's original position (asterisk) (bar indicates 10 μm).

The corneas from donor eyes on which posterior chamber intraocular lens implantation had been performed also showed an irregular F-actin pattern. Tightly packed aggregates of F-actin fibers were observed to accumulate along the cellular borders. In some cells, the F-actin was located in dense focal aggregates while most cells were in their normal hexagonal array with the F-actin located circumferentially (Fig. 6).

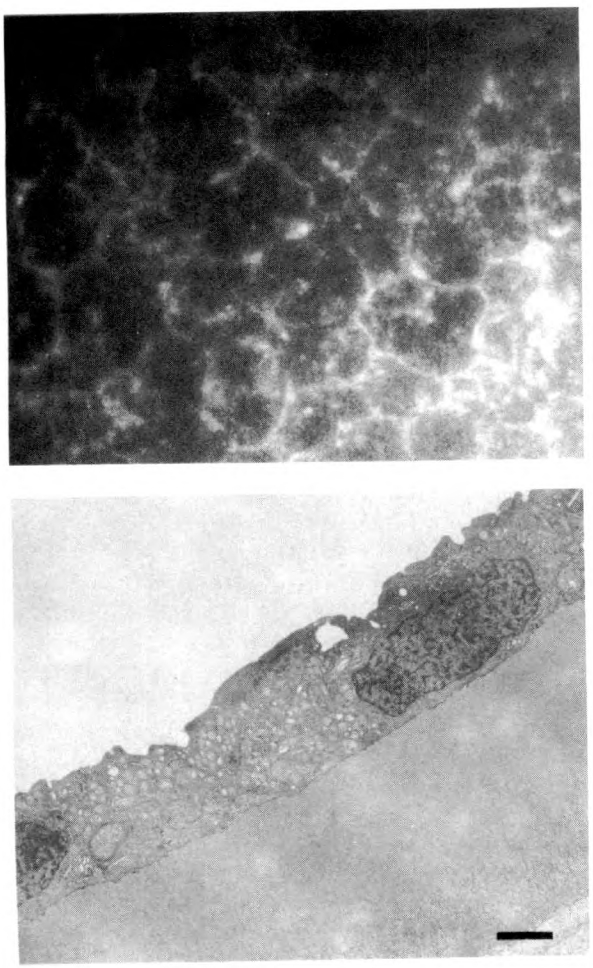
The corneal endothelium of diabetic individuals showed severe polymegethism and, although cellular F-actin showed a prominent circumferential pattern, many F-actin fibers randomly crossed the cytoplasm. These changes were noted throughout the endothelium (Fig. 7). Scattered F-actin fibers were not observed in the cytoplasm of normal human corneal endothelial cells.

Discussion

F-actin, which is assembled through the polymerization of G-actin, is a major component of the cellular cytoskeleton. The polymerization of G-actin is inhibited by the cytochalasin,[15] although the extent of inhibition might be different between rabbit and human tissue. The results of the cytochalasin perfusion studies showed that the F-actin is important in maintaining cell shape and barrier function of the corneal endothelium. Disruption of F-actin with cytochalasin D perfusion resulted in elongated and disarranged cell shape and increased permeability of the rabbit corneal endothelium, indicating endothelial cell dysfunction.

The disruption of the F-actin that occurs with cytochalasin exposure was greater and more severe in the rabbit than in the human endothelium. This suggests that the F-actin component of the human endothelial cytoskeleton has a greater resistance to cytochalasin D than that of the rabbit. This difference may be related to the difference of F-actin turnover rate. For example, the rabbit F-actin may have a much faster turnover rate than that of human F-actin; thus, the rabbit F-actin would be more sensitive than the human F-actin. However, other differences in cytoskeletal composition may exist between rabbit and human corneal endothelium.

F-actin has an important role in the endothelial wound healing process. Fujino and Tanishima[7] studied F-actin changes in the rabbit corneal endothelium after transcorneal freezing. They showed the development of fiber-like F-actin structures three days after injury. F-actin structures having a punctate pattern scattered throughout the cytoplasm 14 days after injury were described. As the endothelium healed completely, the F-actin pattern returned to nor-



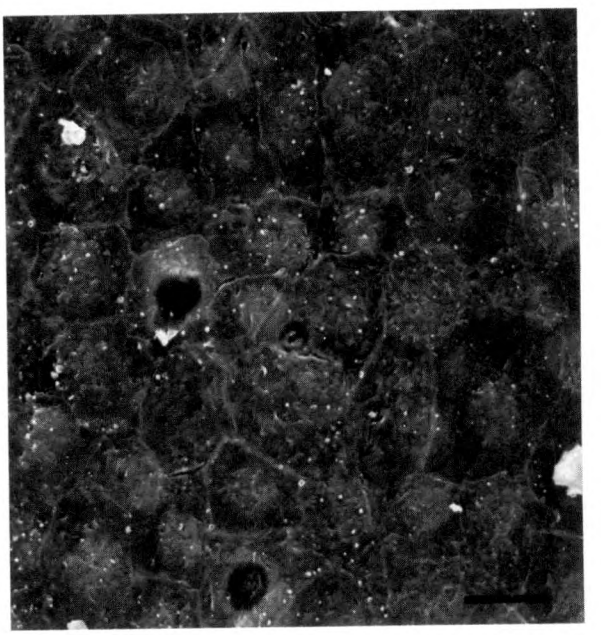


Fig. 4 (Kim and associates). Human corneal endothelium after perfusion with cytochalasin D (5 μg/ml) for one hour. Top left, Nitrobenzoxadiazole-phallacidin staining shows that F-actin has a predominantly hexagonal pattern (×480). Top right, Scanning electron microscopy shows an intact endothelial monolayer and cell junctions were preserved (bar indicates 10 μm). Bottom left, Transmission electron microscopy shows a relatively normal monolayer except for some irregularity of the anterior endothelial cell surface (bar indicates 2 μm).

mal. In our study, the endothelium of a donor cornea after cataract extraction with posterior chamber intraocular lenses implantation showed regions of a punctate pattern of F-actin similar to that described by Fujino and Tanishima.[7] Other areas of the endothelium remained normal. Because of the limited proliferative capacity of human tissue, this punctate pattern might persist and such changes might indicate a corneal endothelium in the process of focal wound healing. Watsky, McDermott, and Edelhauser[13] found that the corneal endothelial permeability to carboxyfluorescein was increased in all donor eyes on which previous intraocular surgical procedures had been performed. The observed increase in permeability may reflect the focal wound healing and cytoskeletal changes observed in these eyes.

Our studies showed many F-actin fibers crossing the cytoplasm of the corneal endothelium of diabetic individuals, compared to small changes of endothelial cellular F-actin at the

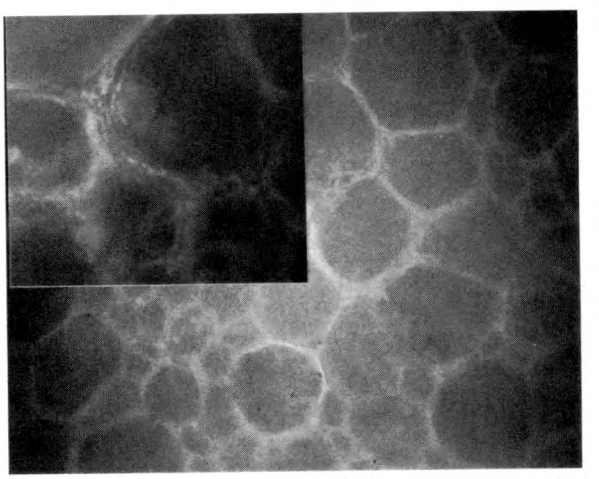


Fig. 5 (Kim and associates). Nitrobenzoxadiazole-phallacidin–stained corneal endothelium with severe polymegethism from a 77-year-old woman. Though all F-actin fibers remain associated with the circumferential cytoskeleton, increased fiber complexity along the cell membrane can be noted (×250; inset, ×630).

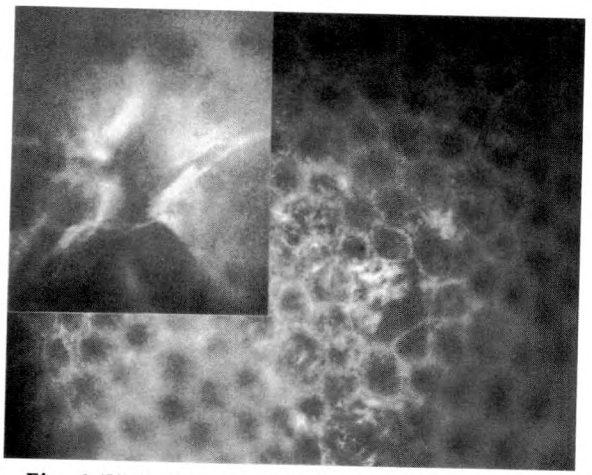


Fig. 6 (Kim and associates). Corneal endothelium of an 81-year-old woman after posterior chamber intraocular lens implantation. Nitrobenzoxadiazole-phallacidin staining shows focal areas of irregular F-actin and the formation of dense aggregates. Most other cells, however, are in normal hexagonal array, with the F-actin located in its normal circumferential pattern (× 250; inset, × 630).

borders between adjacent cells in corneas with endothelial polymegethism in nondiabetic patients. Kleinzeller and Ziyadeh[16] described marked swelling of shark rectal gland cells treated with the organic mercurials, which are known to induce a dissociation of F-actin. They also showed that hypotonicity induced by reduction of the sodium concentration in the media resulted in a loss of cellular F-actin, and massive cellular swelling. They hypothesized that the resistance of the cell membrane to stretch, imparted by the intact cytoskeleton, has a major role in restricting cellular swelling caused by osmotic forces. In the corneas of diabetic individuals, in which there were changes in the F-actin, the changes may have been related to the sorbitol accumulation in the endothelial cell and osmotic gradient between the endothelial cell cytoplasm and aqueous humor. If the corneal endothelium is under continual osmotic stress, an F-actin change to the cell cytoskeleton is most likely to occur to prevent rupture of the cell membrane.[16,17] Since the osmotic stress induced in the corneal endothelium of diabetic individuals occurs over a long time period, leading to polymegethism, the endothelial cell changes appear to be a permanent alteration to the cytoskeleton. Polymegethism develops in corneas with aging, diabetes, after a surgical procedure or infection, and with contact-lens wear. In corneal endothelia with polymegethism in nondiabetic individuals, there were small, but definite changes in F-actin in the borders between adjacent cells. These changes may suggest that the endothelial cells are in stress, but can maintain their structure and can resist cellular swelling with minimal changes in F-actin. Rao and associates,[3] however, demonstrated that after cataract extraction, patients with an endothelium with polymegethism had significantly higher corneal thickness than patients who had a regular endothelial cell pattern. Schultz and associates[18] studied polymegethism in corneas of diabetic individuals with quantitative

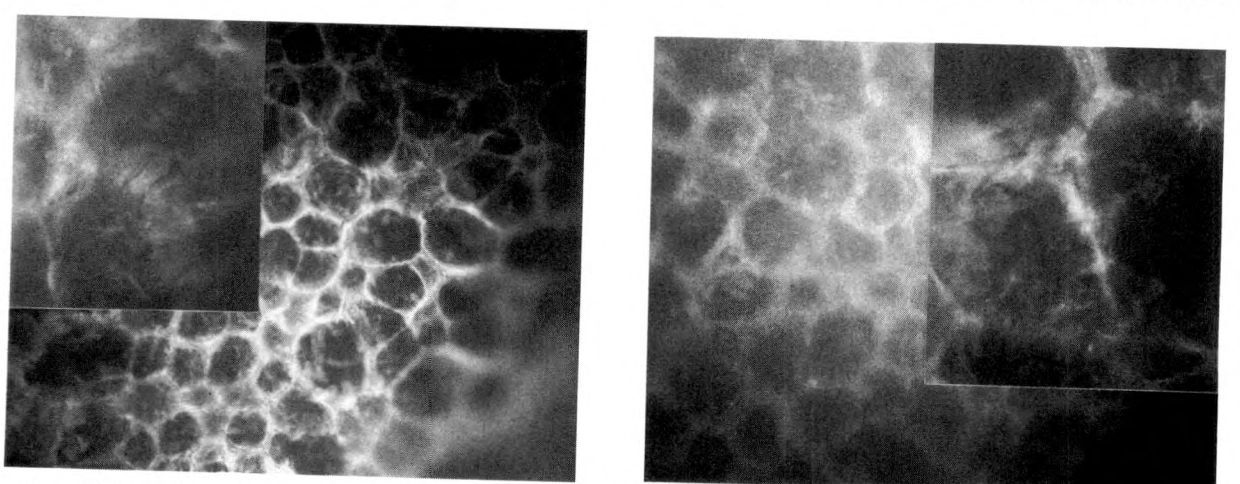


Fig. 7 (Kim and associates). In donor corneas of diabetic individuals, nitrobenzoxadiazole-phallacidin staining shows many F-actin fibers randomly crossing the cytoplasm. Left, Endothelium with severe polymegethism from a 77-year-old diabetic woman (× 250; inset, × 630). Right, Endothelium with moderate polymegethism from a 65-year-old diabetic man (× 250; inset, × 630).

morphometry and suggested that the corneas of diabetic individuals may be at risk in any intraocular procedure. Our data also showed that an endothelium with polymegethism has an altered cytoskeleton and, thus, might be more vulnerable to trauma from intraocular surgical procedures.

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Ciprofloxacin-resistant Bacterial Keratitis

Michael E. Snyder, M.D., and Harold R. Katz, M.D.

Ciprofloxacin, a new broad-spectrum antibiotic effective against a variety of gram-positive and gram-negative bacteria, has recently become available in topical ophthalmic solution (3 mg/ml) for the treatment of bacterial keratitis. It has rapidly become the drug of choice in treating bacterial keratitis. We treated three patients with bacterial corneal ulcers that were resistant to ciprofloxacin, yet were effectively treated with other topical antimicrobial agents. The initial culture results are important in the therapy of corneal ulcers.

CIPROFLOXACIN is the most active of the new class of fluorinated quinolone antibiotics.[1] It has recently become commercially available in a 0.3% ophthalmic solution. Because ciprofloxacin is a single, readily available broad-spectrum antibiotic active against both gram-positive and gram-negative organisms, it is becoming a first-choice drug in the treatment of bacterial corneal ulcers. Within the last five months, we treated three patients with bacterial keratitis at the Krieger Eye Institute in whom ciprofloxacin therapy failed and who were culture positive for ciprofloxacin-resistant organisms. Two patients were treated with ciprofloxacin solution (Ciloxan, Alcon Laboratories, Fort Worth, Texas), whereas the third patient was treated initially with ciprofloxacin 0.3% ophthalmic ointment as part of an ongoing study with Alcon Laboratories. All three patients were successfully treated with conventional fortified antibiotics.

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From the Krieger Eye Institute, Sinai Hospital of Baltimore (Drs. Snyder and Katz), and Wilmer Ophthalmological Institute, Johns Hopkins Hospital (Dr. Katz), Baltimore, Maryland.

Reprint requests to Harold R. Katz, M.D., Krieger Eye Institute, Department of Ophthalmology, Sinai Hospital of Baltimore, Belvedere at Greenspring, Baltimore, MD 21215-5271.

Case Reports

Case 1

A 67-year-old man underwent bilateral upper-eyelid levator aponeurosis repair for blepharoptosis. On postoperative day 1, he had severe conjunctival chemosis with conjunctival prolapse that prevented closure of his eyelids. Despite an aggressive treatment regimen of hourly lubrication with ointment, the patient's corneal epithelium appeared to be irregular on the next day, though no staining defects were noted. Tobramycin 0.3% ointment was added four times daily for prophylaxis, which the patient used only once because of discomfort. The next day he had three small areas of inferior paralimbal moderately dense corneal stromal infiltrates with overlying epithelial defects. Corneal scrapings and cultures were performed and the patient was given ciprofloxacin 0.3% ophthalmic solution hourly. One day later, the infiltrate worsened and 24-hour culture results disclosed methicillin-sensitive *Staphylococcus epidermidis* resistant to ciprofloxacin and sensitive to cefazolin (Table). The patient's treatment was switched to topical cefazolin 50 mg/ml, hourly, and the infiltrate resolved and the corneal epithelium healed within the next three weeks.

Case 2

A 63-year-old woman with a central corneal ulcer was referred to the Krieger Eye Institute. The patient had undergone previous uncomplicated extracapsular cataract extraction for a mature cataract several years earlier. Her postoperative visual acuity was counting fingers because of diabetic retinopathy. Examination disclosed a dense stromal infiltrate with an overlying epithelial defect. Cultures and scrapings of the ulcer were performed. The patient was treated with ciprofloxacin 0.3% ointment every two hours according to the protocol in an ongoing investigation with Alcon Laboratories on the safety and efficacy of ciprofloxacin oint-

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TABLE
SENSITIVITIES TO ORGANISMS CULTURED FROM BACTERIAL KERATITIS*

	STAPHYLOCOCCUS EPIDERMIS MIC_{90} (μg/ml)		*XANTHOMONAS MALTOPHILA* MIC_{90} (μg/ml)
ANTIBIOTIC	CASE 1	CASE 2	CASE 3
Amikacin	—	—	> 32 R
Cefazolin	≤ 1 S	4 R	—
Ceftazidime	—	—	8 S
Ceftriaxone	—	—	> 32 R
Chloramphenicol	> 16 R	8 S	—
Ciprofloxacin	> 2 R	> 2 R	> 2 R
Clindamycin	< 0.12 S	0.25 S	—
Gentamicin	> 8 R	> 8 R	> 8 R
Oxacillin	< 0.5 S	> 6 R	—
Penicillin	> 8 R	> 8 R	—
Ticarcillin	—	—	8 S
Tobramycin	4 S	—	> 8 R
Vancomycin	2 S	2 S	—

*S denotes sensitive; R denotes resistant; a dash indicates not tested.

ment in the treatment of bacterial keratitis. In the protocol of that study, patients are treated with ciprofloxacin ointment every two hours for the first 48 hours, and then every four hours at the discretion of the investigator. The corneal infiltrate improved on the first and second days after initiation of therapy and ciprofloxacin crystals were present on the stromal surface. The 48-hour culture results disclosed coagulase-negative *S. epidermidis* that was resistant to both cefazolin and ciprofloxacin, and that was sensitive to vancomycin (Table). Because of the initial favorable response to ciprofloxacin, the treatment with ciprofloxacin ointment was continued for 12 days. When the corneal infiltrate failed to improve further, the patient's treatment was switched to topical vancomycin solution (50 mg/ml) every hour with a subsequent taper regimen. The patient's infiltrate cleared and the corneal epithelium healed within the next 12 days.

Case 3

A 53-year-old woman with a visual acuity of no light perception in the left eye because of uveitic glaucoma had a one-week history of pain and discharge from her blind left eye. Examination of the right eye disclosed a visual acuity of 20/25, a small hypopyon, and a mild vitreitis with perivenous sheathing of the retinal vessels. Examination of the left eye disclosed moderate conjunctival injection, moderate discharge, a 4 × 5-mm dense central stromal infiltrate with an overlying epithelial defect, and a 2-mm hypopyon. Her medications at that time were timolol 0.5% instilled in the left eye twice daily and prednisolone acetate 1% applied to the left eye twice daily. Corneal scrapings and cultures were performed, and the patient was treated hourly with ciprofloxacin 0.3% ophthalmic solution, three times a day with atropine sulfate 1% to both eyes, and twice a day with 40 mg of prednisone. Bacterial corneal ulcer in the left eye and Behçet's disease were diagnosed. The patient's corneal infiltrate did not improve over the next two days. The 48-hour culture results disclosed *Xanthomonas maltophila* resistant to ciprofloxacin and sensitive to ticarcillin (Table). When therapy was changed to hourly ticarcillin drops (4.1 mg/ml), the patient showed rapid initial improvement followed by gradual improvement over three weeks, but subsequently the epithelium failed to heal and progressed to perforation.

Discussion

The fluorinated quinolone antibiotics were first introduced for the treatment of systemic infections in the late 1980s.[1] Their use rapidly increased for the treatment of many systemic infections varying in severity from severe life-threatening infections to fairly minor infections, such as uncomplicated urinary tract infections. Initial experience with ciprofloxacin was positive and, although it remains a useful antibiotic for many severe infections, several resistant organisms have been detected.[2-4]

The quinolones have more recently been introduced to ophthalmology and appear to be effective in the treatment of corneal ulcers. Experimental animal studies[5,6] and more recent clinical trials[7] have shown that ciprofloxacin is an effective agent for infectious keratitis caused by a variety of organisms including methicillin-resistant *Staphylococcus* species. It also appears to be effective in the treatment of experimental endophthalmitis (unpublished data from our laboratory, 1991).

Ciprofloxacin offers the advantages of com-

mercial availability, use as a single broad-spectrum agent, and greater potency in comparison to other commercially available antibiotics. Leibowitz[7] found an overall clinical success in 91.9% of 148 corneal ulcers treated with ciprofloxacin. Insler and associates[8] reviewed two cases of methicillin-resistant *S. aureus* keratitis that were managed successfully with ciprofloxacin. Ciprofloxacin has rapidly become the drug of choice in microbial keratitis for many clinicians and is the only Food and Drug Administration–approved treatment for bacterial keratitis. Unlike a commercially prepared eyedrop, the potential complications of fortified pharmacy-prepared solutions are well known, such as epithelial toxicity, pH variation of the solutions, and contamination with virulent organisms.[8-11] The variable shelf life of hospital pharmacy–prepared solutions also may limit the effectiveness of therapy.[12,13]

At our institution we have been using ciprofloxacin to treat patients with bacterial keratitis since August 1989, and it has been our drug of choice since it became commercially available. Overall, our results with ciprofloxacin have been excellent[7]; however, the three cases of this study demonstrate that ciprofloxacin-resistant organisms exist. Although satisfactory results may occasionally be achieved with antibiotics to which the cultured organisms show in vitro resistance,[10] the poor clinical response in our cases was in accordance with the in vitro resistance of the cultured organism. Also, after treatment with antimicrobial agents that displayed in vitro activity to the cultured organism, clinical improvement was rapid. We attribute the ultimate failure of treatment in Case 2 to the high-dose oral corticosteroid treatment that was required to treat the contralateral eye (right eye) adequately, which retained useful vision.

Although ciprofloxacin appears to be an excellent broad-spectrum antibiotic that can be used as the initial therapy in bacterial keratitis, initial cultures are vital in the treatment of bacterial corneal ulcers and antimicrobial agents may need to be modified in specific cases depending on the clinical response and the antibiotic sensitivities of the bacteria cultured.

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Paraformaldehyde-induced Keratitis After Photorefractive Keratectomy

Ioannis G. Pallikaris, M.D., Miltiades K. Tsilimbaris, M.D., Maria E. Papatzanaki, M.D., Konstantinos G. Goles, M.D., and Dimitrios S. Siganos, M.D.

We examined three patients who developed keratitis after myopic photorefractive keratectomy. All patients were treated on the same day and in all three cases paraformaldehyde tablets were used for disinfection of the excimer laser iris cone. All patients developed an intense postoperative corneal inflammation that resulted in corneal opacities. In the first patient, the opacities were central and persisted for at least 4½ months postoperatively. He became more myopic than before the operation. His best spectacle-corrected visual acuity worsened by four Snellen lines. In the other two patients, the corneal opacities were paracentral and of less density. Six months postoperatively, these opacities were barely seen. In these two patients, the postoperative best spectacle-corrected visual acuity remained unchanged or improved one Snellen line compared to the preoperative level. In all three patients, astigmatism increased postoperatively. These observations suggest that paraformaldehyde tablets are not safe for the disinfection of the excimer laser iris cone.

PARAFORMALDEHYDE is a solid polymer of formaldehyde, a gas used for disinfection and sterilization of certain types of surgical, medical, and laboratory equipment. At room temperature (20 to 28 C), paraformaldehyde gradually gives off gaseous formaldehyde. Gaseous formaldehyde destroys bacteria within one or two hours. Viruses are also killed.[1] We examined three patients in whom intense keratitis developed after excimer laser photorefractive keratectomy for the correction of myopia. In each case, paraformaldehyde tablets were used for disinfection of the fixation-suction ring, which is integrated with the excimer laser iris diaphragm.

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From the Department of Ophthalmology, Division of Medicine, School of Health Sciences, University of Crete, Greece. This study was presented in part at the Excimer Laser Meeting, Heraklion, Crete, Greece, Nov. 1–3, 1991.

Reprint requests to Ioannis G. Pallikaris, M.D., University of Crete, School of Health Sciences, Division of Medicine, Dept. of Ophthalmology, 714 09 Heraklion, Crete, Greece.

Patients and Methods

Three patients underwent standard photorefractive keratectomy for the correction of myopia in which a 193-nm excimer laser (Phoenix, Aesculap-Meditec GMBH, D-8501 Heroldsberg, Germany) was used. The laser operated in a scanning-slit mode (repetition rate, 20 Hz; fluence at the cornea, 220 mJ/cm^2). The optical zone was 5 mm in diameter. The magnitude of the correction was programmed by a computer that controlled both the total ablation time and the movement of a mechanical iris over the treated area. The cone that contained the mechanical iris was fixed on the globe by a suction ring that immobilized the eye. Disinfection of the mechanical iris was achieved by placing it in a plastic container in which two to three paraformaldehyde tablets (paraformaldehyde, 1 g, for disinfection by fumigation, MERK, E. Merk, D-6104 Darmstadt, Germany) were added, two or more hours preoperatively.

Informed consent was obtained from each patient after a thorough description of the procedure and its risks.

Before laser treatment, the corneal epithelium was softened by using cocaine 2% eyedrops. The optical axis was marked and the epithelium was removed by means of a hockey knife within a 6-mm-diameter area. The exposed corneal surface was irrigated with buffered saline solution. The iris cone was then

placed on the cornea and fixed by using the suction ring. Photorefractive keratectomy was then performed. After the procedure, the ablated area was carefully cleaned with a cellulose sponge. The eyes were patched until reepithelialization occurred.

Postoperative examination included a slit-lamp examination (and photography), keratometry, corneal topography, and autorefraction. Both uncorrected and best spectacle-corrected visual acuity were determined, after reepithelialization had occurred.

Postoperatively, the subepithelial haze was graded by using the gradation scheme described by Fantes and associates.[2] In this scheme, haze is graded as follows: grade 0, cornea totally clear; grade 1, haze seen with difficulty with direct and diffuse illumination; grade 2, mild haze easily visible with direct focal slit-lamp illumination; grade 3, iris details partially obscured; and grade 4, dense opacity completely obscuring the details of intraocular structures.

Case Reports

Case 1

A 31-year-old man underwent standard photorefractive keratectomy for the correction of 4 diopters of myopia in his right eye. He had been myopic since childhood and had worn hard contact lenses for the previous 20 years. He had a history of mild allergic conjunctivitis.

His preoperative visual acuity was 20/100 without correction and 20/25− with the best spectacle correction. The autorefraction reading was −3.0 −1.25 × 10 and the subjective refraction was −3.75 −1.75 × 175. The keratometric reading was 41.3/42.6(67).

Paraformaldehyde dust was observed on the surface of the cone before application of the iris cone to the eye. The dust was carefully removed by using air flow and mechanical wiping with a cellulose sponge. On the first postoperative day, the patient had intense ocular pain. At slit-lamp examination, the cornea was edematous and cloudy and was more pronounced in the anterior stroma adjacent to the ablated area. Descemet's folds and a moderate flare (not obscuring the details) were seen in the anterior chamber. At that time, only patching was used. On postoperative day 4, no improvement was noted and cultures were performed (Fig. 1). Topical treatment with fortified antibiotics



Fig. 1 (Pallikaris and associates). Case 1. Slit-lamp photograph three days postoperatively showing intense corneal inflammation.

(gentamicin sulfate and cefazolin sodium, every half an hour) was started and the eye remained unpatched. The culture results were negative and the clinical signs and symptoms did not change with the antibiotic therapy. Furthermore, during the first postoperative days, minute opaque dots in the anterior corneal stroma were observed when using high magnification. These dots gradually disappeared and, at the end of the third postoperative week, were no longer visible. The cause of the corneal inflammation was attributed to the paraformaldehyde dust that was noticed intraoperatively. On postoperative day 20, the treatment was changed to daily dexamethasone sodium phosphate subconjunctival injections; tobramycin sulfate eyedrops, twice daily; and tear substitute in gel, twice daily, while the eye remained patched. The new treatment was more effective, as the corneal edema, as well as Descemet's folds, gradually subsided.

On postoperative day 50, the cornea was fully reepithelialized. There was still a mild stromal edema and a subepithelial haze of grade 3 density throughout the ablated area. An opacity of the anterior stroma was seen in the center of the ablated area. His visual acuity was 20/64 without correction and 20/32 with best spectacle correction. The patient had to hold his head in an oblique position to attain his best visual acuity. The autorefraction reading was −0.25 −5.75 × 43. Keratometry disclosed irregular images. The patient began treatment with topi-

cal prednisolone acetate and tobramycin sulfate eyedrops, six times daily. One week later, the corneal edema had resolved. His visual acuity was 20/64 without correction and 20/32 with best spectacle correction, always with an oblique position of the head. The autorefraction reading was −2.75 −3.75 × 23 and the keratometric reading was 38.25/40.75(120). The patient described his vision as blurred.

Four and one-half months postoperatively, his visual acuity was 20/200 without correction and 20/50 with best spectacle correction (with oblique head position). The autorefraction reading was −7.5 −2.25 × 3, the subjective refraction reading was −5.0 −2.5 × 180, and the keratometric reading was 43.25/45.5(80). The cornea was normally epithelialized and uninflamed. However, a central corneal scar could be easily detected. There was a grade 2 to 3 reticulate subepithelial haze throughout the ablated area (Fig. 2).

Corneal topography disclosed a central corneal flattening immediately after epithelialization that disappeared 15 days later. On his last visit, 4½ months postoperatively, the central cornea was steeper than before photorefractive keratectomy.

Case 2

A 26-year-old woman underwent standard photorefractive keratectomy for the correction of 7 diopters of myopia in her right eye. She had been myopic since childhood and had worn contact lenses for the previous seven years. Her preoperative visual acuity was counting fingers at 3 m without correction and 20/200 with best spectacle correction. The autorefraction reading was −5.75 −1.25 × 5, the subjective refraction reading was −6.0 −1.75 × 180, and the keratometric reading was 43.75/45.25(91).

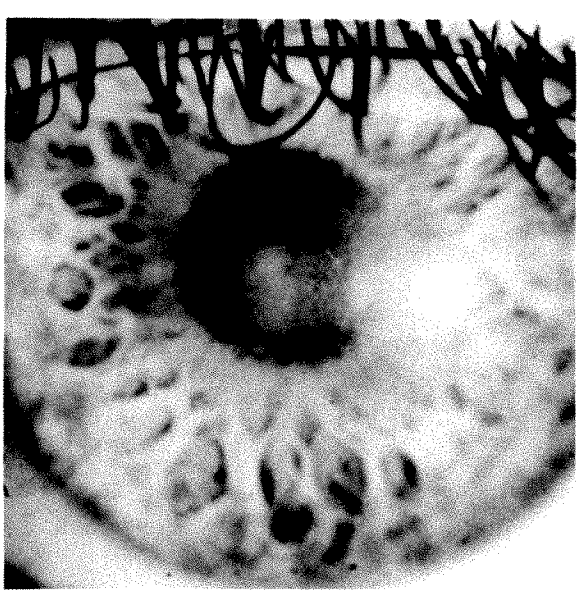


Fig. 2 (Pallikaris and associates). Case 1. Slit-lamp photograph 4½ months postoperatively showing subepithelial haze and central opacity.

Immediately before application of the cone to the patient's eye, paraformaldehyde dust was seen on the cone surface and was carefully removed by using air flow and mechanical wiping with a cellulose sponge.

On postoperative day 5, the cornea was reepithelialized. There was stromal edema, as well as a paracentral opacity of the anterior stroma. A grade 2 subepithelial haze could also be seen. Prednisolone acetate and tobramycin sulfate eyedrops were instilled five times daily. Four days later, the corneal edema had resolved, but the opacity and the subepithelial haze did not change. Her visual acuity was 20/40 without correction and 20/25− with best spectacle correction. The keratometric reading was 38.5/41.75(95) and the autorefraction reading was −2.0 × 170.

Four months postoperatively, the cornea remained well epithelialized with a less intense paracentral opacity of the anterior stroma. The subepithelial haze was graded 1. Her visual acuity was 20/32 without correction and 20/20 with best spectacle correction. The autorefraction reading was −0.25 −3.0 × 175 and the keratometric reading was 40.0/42.5(85).

Six months postoperatively, her visual acuity was 20/32 without correction and 20/20 with best spectacle correction. The keratometric reading was 40.5/42.75(85), the autorefraction reading was −0.75 −2.5 × 175, and the subjective refraction reading was −0.75 −2.5 × 175. The paracentral corneal opacity was barely seen and the subepithelial haze was graded 1 (Fig. 3).

Case 3

A 52-year-old woman underwent standard photorefractive keratectomy for the correction of 7 diopters of myopia in her left eye. She had been myopic since childhood and had never worn contact lenses. Her uncorrected preoperative visual acuity was 20/200 and 20/25− with best spectacle correction. The autorefraction reading was −7.5 −2.5 × 180, the subjective refraction reading was −7.0 −2.75 × 2, and the keratometric reading was 43.5/47.1(85).

We removed the paraformaldehyde dust from

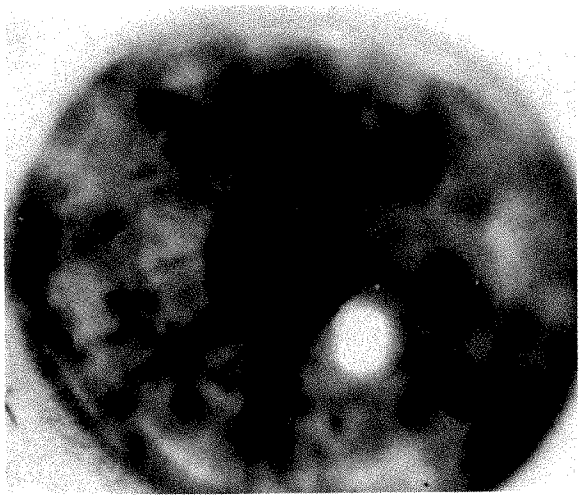


Fig. 3 (Pallikaris and associates). Case 2. Slit-lamp photograph six months postoperatively. The corneal haze is hardly seen.

the cone surface before the procedure in the previously discussed manner. On postoperative day 5, the patient had a car accident and for this reason her data on refraction were incomplete. The cornea was reepithelialized on postoperative day 8. There was stromal edema and a paracentral opacity of the anterior stroma. A grade 2 subepithelial haze could be seen. She started treatment with topical prednisolone acetate and tobramycin sulfate drops six times daily. Forty days postoperatively, her visual acuity was 20/64 without correction and 20/32− with best spectacle correction. The autorefraction reading was −1.75 −4.5 × 180 and the keratometric reading was 39.25/42.1(93). A paracentral corneal opacity and a grade 2 subepithelial haze were also observed.

Six months postoperatively, her visual acuity was 20/50 without correction and 20/20 with best spectacle correction. The autorefraction reading was −1.5 −3.25 × 10, the subjective refraction reading was −1.75 −3.5 × 10, and the keratometric reading was 39.75/43.75(92). A grade 1 subepithelial corneal haze and a paracentral opacity in the anterior corneal stroma of much less density than in her previous visits could be seen.

Discussion

The three patients were among the first at our clinic to be operated on with the excimer laser for the correction of myopia. As the mechanical iris cone was the only part of the laser that was in contact with the patient's eye and because autoclaving was impossible, we used paraformaldehyde tablets for disinfection of the cone. The three patients underwent the operation on the same day in the order in which they were examined. The iris cone remained in the container with the paraformaldehyde tablets for 24 hours before the first operation, and for two hours before each of the next two operations. A small amount of paraformaldehyde dust could be seen on the cone surface at the end of the disinfection. Before applying the suction ring on the patient's eye, the paraformaldehyde dust was carefully removed. However, the mechanical closure of the iris blades, as well as the air flow around the iris and suction ring, probably released incarcerated paraformaldehyde dust on the ablated corneal surface. At the end of the procedures, no paraformaldehyde dust could be detected on the ablated area. This should be expected, as the chemical spreads rapidly through the entire thickness of the stroma after its application on the cornea.

Postoperatively, all three patients developed intense corneal inflammation, which lasted 50 days in the first patient. The other two patients recovered earlier. In all three patients, opacities developed in the anterior stroma. In the first patient, the corneal opacity was central and accompanied by a grade 2 to 3 reticulate haze. The final result was a 4-Snellen-line reduction of his best-corrected visual acuity. The other two patients developed a paracentral opacity that did not interfere with the final visual acuity. The more severe reaction observed in the first patient was probably caused by accumulation of more paraformaldehyde dust on the cone surface that resulted from the longer disinfection time.

Paraformaldehyde is a polymer of formaldehyde that, in room temperature (20 to 28 C), depolymerizes to formaldehyde; their toxicity is identical.[3] Formalin, the aqueous solution of formaldehyde, has been toxic to the eye in dilutions from 1 in 1,000 to 1 in 2,000. Accidental application of a drop on the cornea results in extreme chemosis and keratitis, which leads to permanent opacities. Formalin experimentally applied to a rabbit cornea spreads rapidly throughout the entire thickness of the stroma; the corneal corpuscles are killed and fixed in situ to appear as minute white dots.[4] This is consistent with our observation of white

opaque dots in the corneal stroma of our first patient.

When paraformaldehyde dust was applied to the ablated area of rabbit corneas immediately after photorefractive keratectomy, it resulted in a severe inflammation, a delay of reepithelialization, and a formation of an intense subepithelial corneal haze (Pallikaris and associates, unpublished data, 1991).

After observing intense corneal reactions, we stopped using paraformaldehyde tablets for disinfecting the iris cone. Of the 30 patients operated on in our clinic with the excimer laser so far, only the three patients of this study developed intense postoperative inflammation and corneal opacities. These patients, as already mentioned, were the first to be operated on and the only in whom paraformaldehyde tablets were used for the iris cone disinfection. Therefore, we believed the intense inflammatory reaction and the corneal opacities were caused by the corneal toxicity of paraformaldehyde.

Currently, we disinfect the lower part of the iris cone, where the suction ring is located, by immersing the cone in isopropyl alcohol solution 70% for 20 minutes. Isopropyl alcohol is a known disinfectant and has been an efficient means of disinfecting Goldmann tonometers against both human immunodeficiency virus type 1 and herpesviruses. There is evidence that 70% isopropyl alcohol also inactivates hepatitis B virus.[5]

The regression of myopia was interesting in our first patient. The preoperative spherical equivalent of this patient was −3.6 diopters. Immediately after reepithelialization, the spherical equivalent was −3.1 diopters, and 4½ months postoperatively, it was −8.6 diopters. This patient had the most intense inflammatory reaction, with the final amount of haze and subepithelial scarring appearing to correspond with the degree of regression. His myopia not only regressed but also actually overshot the preoperative level. This was presumably a result of both corneal remodeling after the intense inflammation and secondary scar formation. Contracture of this scar tissue could lead to steepening of the cornea and regression of the myopic photoablative outcome. This effect, in conjunction with corneal topography measurements, may be interesting regarding the study of regression after photoablative keratectomy. McDonald, Frantz, and Klyce[6] described a case of marked regression after myopic photorefractive keratectomy that was attributed to stromal remodeling. Seiler and Wollensak[7] described marked regression in eyes with marked scarring after photorefractive keratectomy.

All three of our cases also showed an increase in astigmatism. The refractive astigmatism of the first patient was −1.25 × 10 preoperatively, and −2.25 × 3 4½ months postoperatively. The refractive astigmatism of the second patient was −1.25 × 5 preoperatively, and −2.5 × 175 six months postoperatively. Finally, the refractive astigmatism of the third patient was −2.5 × 180 preoperatively, and 3.25 × 10 six months postoperatively. Corneal remodeling after the formaldehyde-induced inflammation was probably the reason for this astigmatic effect.

Postoperatively, all patients were intensively treated with corticosteroids, and at least in the patients in Cases 2 and 3, this therapy was effective in preserving the photoablative myopic correction. This effectiveness may be of interest regarding the effect that the specific corticosteroid treatment regimen may have in modifying the wound healing response and amount of regression.

The perioperative complication observed in these patients dictates careful attention to sterilization of any device that contacts the eye. Once an instrument is cleaned with a disinfectant, there is always a chance to cause corneal damage even if only traces remain. A small amount of paraformaldehyde is enough to cause intense corneal inflammation. Meanwhile, it may be extremely difficult to be sure of complete paraformaldehyde removal after its fumigation; the dust of the chemical may be incarcerated in difficult-to-reach locations, as between the blades of the iris cone, for example.

These observations suggest that paraformaldehyde tablets are not safe for disinfection of the excimer laser iris cone or other accessories used on or around the cornea during excimer laser ablation. Contact of paraformaldehyde dust with the ablated area can lead to intense corneal inflammation, resulting in an undesirable refractive outcome, or even impairment of visual acuity after photorefractive keratectomy.

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OPHTHALMIC MINIATURE

Joan had lovely eyes, grey eyes like her father's that reminded one of the sea. In certain lights they could look almost green, as though a tide were washing over them. When we moved to Hendon, it was true, I did miss the sea. I used to look into Joan's eyes sometimes, when she wasn't looking, and she seemed to give me back a little of the winter seas. Eyes are so vulnerable; they say things that words themselves can't say. I used to feel sad and lost looking into the greyness of Joan's gaze. It was almost a relief when her eyes weakened and she had to wear glasses. It shielded me from all her unspoken reproaches and all the unanswerable questions that lay there.

Lisa St. Aubin de Terán, *Joanna*
London, Virago Press, 1990, p. 244

Optisol Corneal Storage Medium

Richard L. Lindstrom, M.D., Herbert E. Kaufman, M.D., Debra L. Skelnik, B.S., Ronald A. Laing, Ph.D., Jonathan H. Lass, M.D., David C. Musch, Ph.D., Melvin D. Trousdale, Ph.D., William J. Reinhart, M.D., Terry E. Burris, M.D., Alan Sugar, M.D., Richard M. Davis, M.D., Kiminori Hirokawa, M.D., Tessie Smith, M.S., and Judy F. Gordon, D.V.M.

We compared the safety and efficacy of Optisol (Chiron Ophthalmics, Irvine, California), a new corneal storage medium, with McCarey-Kaufman and Dexsol corneal storage media (Chiron Ophthalmics, Irvine, California) and K-Sol corneal storage medium (Cilco, Huntington, West Virginia). Optisol contains dextran, 2.5% chondroitin sulfate, vitamins, and precursors of adenosine triphosphate (adenosine, inosine, and adenine). In in vitro studies, rabbit and human corneas stored in Optisol were thinner after 12 to 14 days at 4 C than tissue stored in other media. Thymidine uptake showed increased mitotic activity in human corneal endothelial cells cultured in Optisol, compared to Dexsol. Specular microscopic fields showed larger areas of visibly intact endothelial cells and ultrastructural examination disclosed fewer structural changes in endothelial cells stored in Optisol, compared to tissue stored in Dexsol. In vivo, no clinical signs of epithelial toxicity or histologic evidence of intraocular inflammation were observed in rabbit eyes in which Optisol drops were instilled four times a day for 14 days. Finally, 51 patients undergoing penetrating keratoplasty with tissue stored in Optisol for one to six days (mean, 3.6 days) were enrolled in an uncontrolled, open-label clinical study. The percentage of clear grafts (93%, 41 of 44 patients examined at three months; and 98%, 42 of 43 patients examined at six months) and endothelial cell loss (5.0% and 11.5% at three and six months, respectively) were comparable to data from previous studies that used tissue stored in other short-term and intermediate-term media. The results suggest that Optisol storage preserves corneal endothelial cells for up to two weeks at 4 C, thereby permitting flexibility in the use of donor tissue for corneal transplantation, and that Optisol storage yields thinner tissue, which may allow for more accurate evaluation and more effective surgical manipulation.

A PRIMARY OBJECTIVE of corneal storage is the maintenance of endothelial viability from the time the donor tissue is harvested until it is transplanted. A secondary objective is the efficient use of donor tissue, which is facilitated by increasing the length of time donor tissue can be stored without loss of endothelial integrity. Early dextran-based storage media, such as McCarey-Kaufman medium (Chiron Ophthalmics, Inc., Irvine, California), provided up to 72

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From the Department of Ophthalmology, University of Minnesota and the Phillips Eye Institute, Minneapolis, Minnesota (Dr. Lindstrom and Ms. Skelnik); LSU Eye Center, Louisiana State University Medical Center School of Medicine, New Orleans, Louisiana (Dr. Kaufman); Department of Ophthalmology, Boston University School of Medicine, Boston, Massachusetts (Drs. Laing and Hirokawa); Department of Ophthalmology, Case Western Reserve University and University Hospitals, Cleveland, Ohio (Drs. Lass and Reinhart); Department of Ophthalmology, W. K. Kellogg Eye Center, University of Michigan, Ann Arbor, Michigan (Drs. Musch and Sugar); Doheny Eye Institute, University of Southern California, Los Angeles, California (Dr. Trousdale); Lions Eyebank of Oregon, Devers Eye Institute, Portland, Oregon (Dr. Burris); Department of Ophthalmology, University of South Carolina, Columbia, South Carolina (Dr. Davis); and Chiron Ophthalmics, Inc., Irvine, California (Ms. Smith and Dr. Gordon). This study was supported in part by U.S. Public Health Service grants EY02580 (Dr. Kaufman), EY01227 and EY05927 (Dr. Laing), and EY02957 (Dr. Trousdale) from the National Eye Institute; the Ohio Lions Eye Research Foundation, Columbus, Ohio (Drs. Lass and Reinhart); and Chiron Ophthalmics, Inc., Irvine, California. Drs. Lindstrom and Kaufman and Ms. Skelnik have proprietary and financial interests in Optisol. Drs. Musch and Trousdale are paid consultants to Chiron Ophthalmics, Inc., Irvine, California. Ms. Smith and Dr. Gordon are employees of Chiron Ophthalmics, Inc.

Reprint requests to Judy Gordon, D.V.M., Director, Clinical Research, Chiron Ophthalmics, Inc., 9342 Jeronimo Rd., Ste. 103, Irvine, CA 92718.

hours of storage at refrigerator temperature (4 C).[1-4] Over the past five years, several studies have shown that media that contain chondroitin sulfate (K-Sol [Cilco, Huntington, West Virginia, no longer commercially available], Chondroitin Sulfate Corneal Storage Medium and Dexsol [Chiron Ophthalmics, Inc., Irvine, California]) can extend this period of safety up to ten days.[5-16] Nevertheless, efforts continue to define optimal levels of chondroitin sulfate, as well as to identify additional constituents that improve endothelial preservation.

We undertook a collaborative series of in vitro, in vivo, and clinical studies of the safety and efficacy of a new corneal storage medium, Optisol (Chiron Ophthalmics, Inc., Irvine, California). Optisol contains both dextran and chondroitin sulfate, as well as other new ingredients to prolong and enhance the survival of the endothelium in storage at 4 C.

Material and Methods

Storage medium—Optisol is a hybrid of K-Sol and Dexsol (Table 1), with nearly twice as much chondroitin sulfate as Dexsol has. Additional constituents include vitamins and precursors (adenosine, inosine, and adenine) of adenosine triphosphate. The medium has been shown to be stable for 24 months. All constituents, including the adenosine triphosphate precursors, remain in solution after four days of storage at 4 C.

In vitro studies—To assess the effect of various storage media on mitotic activity, tissue-cultured adult human corneal endothelial cells were incubated in Optisol or Dexsol that contained radiolabeled thymidine. Tissue culture plates (96-well; Costar, Cambridge, Massachusetts) were seeded with 3×10^3 fourth-passage human corneal endothelial cells suspended in 200 μl of Chondroitin Sulfate Corneal Storage Medium that contained 10% fetal bovine serum to permit cell attachment.[15] The plates were incubated for 24 hours at 35.5 C in a humidified, 5% CO_2 atmosphere. The medium was removed and each well was rinsed once with serum-free minimal essential medium supplemented with Earle's solution and 25-mmol/l N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid buffer, followed by a second rinse with either Optisol or Dexsol. The cells were incubated for 72 hours in 200 μl of the same storage medium that contained 1 μCi of ^{3}H-thymidine, after which the radioactive medium was removed and the cells were rinsed with the same supplemented minimal essential medium, detached

TABLE 1
CONSTITUENTS OF K-SOL, DEXSOL, AND OPTISOL*

CONSTITUENT	K-SOL	DEXSOL	OPTISOL
Base medium	Tissue culture medium 199 and Earle's balanced salt solution	Minimal essential medium	Tissue culture medium 199, Earle's balanced salt solution, and minimal essential medium
Buffer	HEPES	HEPES	HEPES
Antibiotic	Gentamicin	Gentamicin	Gentamicin
Chondroitin sulfate	2.5%	1.35%	2.5%
Dextran	No	1%	1%
Adenosine triphosphate precursors	No	No	Adenosine, inosine, and adenine
Iron	No	No	Yes
Cholesterol	No	No	Yes
L-hydroxyproline	No	No	Yes
Vitamins	No	No	Cobalamin, ascorbic acid, α-tocopherol, D-biotin, calciferol, niacin, pyridoxine, and p-aminobenzoic acid

*No indicates absence and yes indicates presence of constituent in the medium; HEPES indicates N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid.

with 0.5% trypsin, and prepared for liquid scintillation counting. Similar experiments were done using different formulations of Optisol, each of which lacked one of the adenosine triphosphate precursors (adenosine, inosine, or adenine), vitamins, iron, L-hydroxyproline, or cholesterol, to determine the importance of each constituent in promoting mitosis.

Six New Zealand White rabbits were killed, the eyes were enucleated, and the corneas were stored in McCarey-Kaufman medium, Dexsol, or Optisol for 14 days at 4 C. Four corneas were assigned randomly to each medium. Assessment on days 0, 1, 3, 5, 7, 9, 11, and 14 (performed after warming the tissue to 24 C for 30 minutes) included ultrasonic pachymetry and specular microscopy. Rabbits were used in accordance with the Association for Research in Vision and Ophthalmology Resolution on the Use of Animals in Research.

For measurement of endothelial cell membrane potential, rabbit eyes were enucleated and the corneas were excised with a 2-mm scleral rim by means of standard eye-bank techniques. The corneas were mounted in a cornea chamber (Model SVC1, Alcon, Fort Worth, Texas) with the top removed. Microelectrodes were made by pulling glass capillary tubing with a 1-mm outer diameter and an internal filament (WRI Company, New Haven, Connecticut). The tip diameter of the electrodes used was 0.1 to 0.2 μm. The electrode was filled with 3-mol/l KCl, which had a resistance of 40 MΩ. The electrode was attached to a microelectrode holder that had an internal Ag-AgCl wire (E. W. Wright, Guilford, Connecticut) and was moved by a micromanipulator (Ernst Leitz, Inc., New York, New York). Corneal endothelial cells were penetrated atraumatically with the microelectrode, as demonstrated by the observation of a stable signal after penetration. The microelectrode signal was amplified (Model M4 Amplifier, W-P Instruments, New Haven, Connecticut), displayed on an oscilloscope (Tektronix Inc., Beaverton, Oregon), and recorded on a chart recorder (Model EU-205-11, Heath-Zenith, St. Joseph, Missouri). Membrane potentials were measured (in millivolts) on days 0, 1, 3, 5, 7, 9, 11, and 14 after the tissue was warmed to 24 C for 30 minutes.

Redox fluorometry[16] was performed to evaluate metabolic status on days 0, 7, and 14; the results were expressed in terms of the ratio of the autofluorescence of reduced pyridine nucleotides to that of oxidized flavoproteins, and calculated for days 7 and 14 as a percent of the value obtained on day 0. On day 14, all tissue was prepared for transmission electron microscopy, as described for human tissue.

A total of ten human corneas (two in each medium) were stored at 4 C for 12 days in 20 ml of either Dexsol or one of four variants of Optisol that contained different concentrations of chondroitin sulfate (1.5%, 1.75%, 2.0%, or 2.5%). Donor age ranged from 65 to 72 years. The corneoscleral rims were dissected from whole globes, which had been decontaminated in 1% povidone iodine solution and rinsed in normal saline solution, and placed in the designated storage medium. Corneal thickness was measured on days 0, 1, 4, 7, and 12 by means of an upright microscope (Leitz, Inc., Rockleigh, New Jersey) fitted with a micrometer; for this process, the tissue was transferred to a petri dish that contained 15 ml of minimal essential medium supplemented with 25-mmol/l N-2-hydroxyethylpiperazine-N′-2-ethanesulfonic acid buffer and Earle's solution and maintained at 4 to 8 C. Three central readings were obtained for each cornea, the readings for all tissue in a given medium at a given time point were combined, and the means and standard deviations were calculated.

On day 12, after the final corneal thickness measurements at 4 to 8 C, the corneas were placed in a 34 C environment, and corneal thickness was measured 30, 60, and 120 minutes thereafter. Again, three central readings were obtained for each cornea, and the means and standard deviations were calculated.

Finally, corneas were equilibrated to room temperature (24 C) and endothelial viability was assessed by staining with 1% trypan blue. Alizarin red S was used to evaluate the integrity of the endothelial cell membranes and the endothelial sheet.

For ultrastructural studies, 18 pairs of corneas not suitable for transplantation from donors 22 to 85 years old were obtained from whole globes after decontamination. The left cornea of each pair was stored in Optisol and the right cornea was stored in Dexsol at 4 C. At intervals after storage, paired corneas were selected and prepared for scanning and transmission electron microscopy. Corneas were selected on the basis of clarity and donor age. Storage times and donor age were as follows: 24 hours or less, 41 and 58 years; day 3, 49 years; day 5, 25 and 47 years; day 7, 22 years; and day 14, 85 years. Specimens selected for examination were washed in 0.1-mol/l sodium cacodylate buffer and fixed in half-strength Karnovsky's solution

for two hours. Samples were then postfixed for 30 minutes in 2% osmium tetroxide, washed with distilled water, and dehydrated through a graded series of ethanols. Half of each specimen was critical-point dried (Autosamdri-814, Rockville, Maryland), sputter coated (Hummer V, Alexandria, Virginia), and mounted for viewing in a scanning electron microscope (Hitachi S-570, Tokyo, Japan). The other half was embedded in plastic (Eponate-12, Ted Pella, Inc., Perkasie, Pennsylvania). Ultrathin sections (LKB V, Deerfield, Illinois) were stained with uranyl acetate and lead citrate and viewed in a transmission electron microscope (AEI EM-801, Harlow, Essex, England).

In vivo studies—Epithelial toxicity in rabbit eyes was evaluated by means of the standard methodology of the Draize, Woodard, and Cavery test.[17] Two drops of Optisol (50 μl each) were instilled in one eye of each of six New Zealand White rabbits every two hours for a six-hour period (total of eight drops) every day for 14 consecutive days. For comparison, 0.9% sodium chloride solution was instilled in one eye of each of six additional rabbits on the same schedule. On day 14, all eyes were examined for irritation one hour after the last instillation on a masked basis by a veterinary ophthalmologist. The next day, the rabbits were killed and the eyes were enucleated with upper and lower eyelids attached, fixed in formalin, and prepared for histopathologic examination.

An uncontrolled, open-label study of human donor corneal tissue stored in Optisol at 4 C before penetrating keratoplasty was conducted at six clinical centers.

Eye banks supplying tissue for this study were asked to store all tissue in Optisol whenever possible, in case the tissue would be needed for this study. Tissue stored initially in another medium was transferred to Optisol when the eye bank was notified that the tissue would be used in a study patient. Eleven corneas were stored in other media before transfer to Optisol (nine in Chondroitin Sulfate Corneal Storage Medium for 15 to 75 minutes, one in minimal essential medium for 30 minutes, and one in Dexsol for four hours 45 minutes). Storage time in Optisol ranged from one to six days, with a mean of 3.6 days (86 ± 34.6 hours, mean ± standard deviation; range, 20 to 154 hours).

The protocol allowed for variable storage time to permit evaluation, over the normal range found in clinical practice, of the possible effect of length of storage on clinical outcomes such as endothelial cell density. The minimum storage time (20 hours) ensured adequate exposure of the corneal tissue to the medium.

Donor information was recorded by the eye-bank technician responsible for harvesting tissue. The mean (± standard deviation) age of the donors was 40 ± 20 years. All tissue was rated good to excellent, except for one rated adequate, before placement in Optisol.

Surgeons were asked to limit the study to patients who required penetrating keratoplasty for pseudophakic or aphakic bullous keratopathy, Fuchs' corneal dystrophy, keratoconus, or avascular failed graft. Informed consent was obtained from each patient enrolled. Epithelial integrity was evaluated preoperatively and one and seven days postoperatively. Central corneal thickness was measured by ultrasonic pachymetry intraoperatively and one, seven, 90, and 180 days postoperatively. Endothelial cell density was estimated by fixed-frame analysis of specular photographs taken preoperatively and 90 and 180 days postoperatively. Graft clarity was evaluated 90 and 180 days postoperatively.

Results

In vitro studies—Fourth-passage human corneal endothelial cells incubated in Optisol for 72 hours incorporated significantly larger amounts of ^{3}H-thymidine (4,348 ± 55.7 counts per minute, mean ± standard error) than cells incubated in Dexsol (3,410 ± 43.0 counts per minute) ($P < .05$). Repeated experiments with cells in Optisol lacking individual constituents showed that the presence of adenosine was the critical factor in this increase in mitotic activity.

Rabbit tissue stored in Optisol was significantly thinner (Fig. 1) over the 14-day storage period, compared to tissue stored in McCarey-Kaufman medium ($P < .004$) or Dexsol ($P < .003$). Specular microscopy showed that, with increasing storage time in all media, the fraction of the fixed-size specular field occupied by visible cells (that is, cells with visible borders) decreased and the area taken up by dark structures increased (Fig. 2). However, more endothelial cells were visible in the specular fields of Optisol-stored tissue (Fig. 3), compared to tissue stored in McCarey-Kaufman medium or Dexsol, after both seven and 14 days of storage.

Despite changes in the specular images, the mean endothelial cell membrane potentials indicated that this measure of membrane penetrability remained relatively stable over the

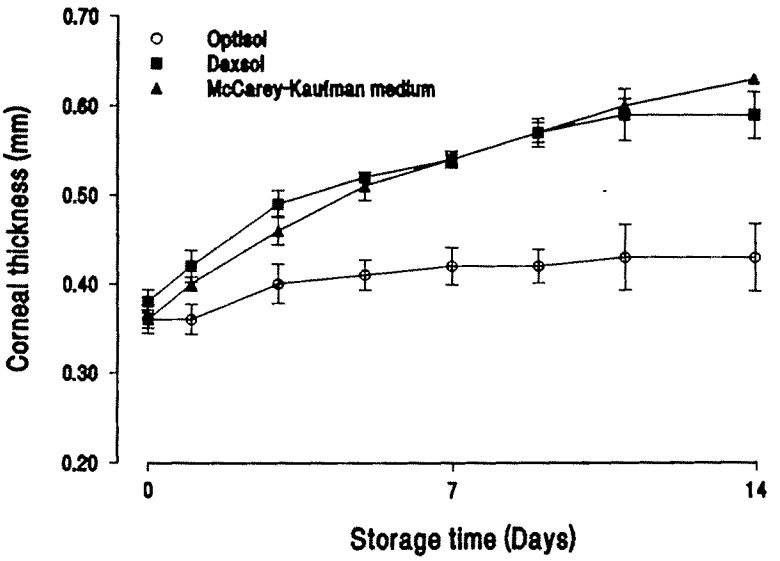


Fig. 1 (Lindstrom and associates). Corneal thickness (measured by ultrasonic pachymetry) for rabbit corneas stored at 4 C for 14 days in Optisol, Dexsol, or McCarey-Kaufman medium. Each point represents the mean ± standard deviation of four corneas.

14-day test period (Fig. 4) in all three storage media. Metabolic equilibrium as measured by the redox potential and plotted as a percent of the value on day 0 (Fig. 5) appeared to show somewhat less decrease in Optisol-stored tissue, compared to tissue stored in McCarey-Kaufman medium or Dexsol, although data were insufficient for statistical analysis. Inspection of this tissue by transmission electron microscopy at the end of the 14-day storage period appeared to show that Optisol-stored tissue had less swollen endothelial cells with fewer cytoplasmic vacuoles than tissue stored in either of the other two media; however, no attempt to quantify these structural findings or to correlate them with measurements of redox potential was made.

Human tissue stored in Optisol that contained 2.5% chondroitin sulfate was significantly thinner after 12 days of storage at 4 C, and after the subsequent two hours at 34 C, than either Dexsol-stored tissue or tissue stored in any of the Optisol formulations with less than 2.5% chondroitin sulfate (Wilcoxon signed rank test, $P < .05$) (Fig. 6). After two hours at 34 C, the 2.5% Optisol-stored tissue was still thinner than any tissue stored in the other media before warming.

Trypan blue and alizarin red S staining showed the endothelial cell layer to be intact and endothelial cell structure to be normal in all specimens (Fig. 7). Corneas stored in media with higher concentrations of chondroitin sulfate did appear to have fewer areas of alizarin red S staining of Descemet's membrane; in general, however, alizarin red S staining was minimal and was confined to areas of stromal folding.

Scanning electron microscopy showed that cellular integrity was maintained in Optisol-stored tissue for three days, whereas tissue stored in Dexsol began to show structural changes on day 3. On day 5, Optisol-stored tissue retained more distinct cell shapes and borders, compared to Dexsol-stored tissue (Fig. 8). By day 7, the Optisol-stored tissue demonstrated less defined cell shapes and by day 14, few intact cell borders and some intercellular spaces. The condition of the Dexsol-stored tissue on day 7 was similar to that of the Optisol-stored corneas on day 14; by day 14, the Dexsol-stored tissue had lost all cellular integrity and cytoplasmic blebs were visible.

Transmission electron microscopy disclosed that on day 5, Optisol-stored tissue showed less sloughing of cellular material from the apical surface of the endothelial cell layer, fewer pinocytotic vesicles, and fewer, smaller cytoplasmic vacuoles, compared to the Dexsol-stored tissue. The basal surface of the endothelial cells stored in Optisol looked normal, whereas these surfaces had an undulating, wavy appearance in the Dexsol-stored tissue (Fig. 9).

In vivo studies—No clinical signs of epithelial irritation were observed in the rabbit eyes in which either Optisol or saline drops were instilled for 14 days or in the untreated contralateral eyes. Histopathologic examination of 5-μm sections of the enucleated eyes disclosed no evidence of inflammation in any of the eyes.

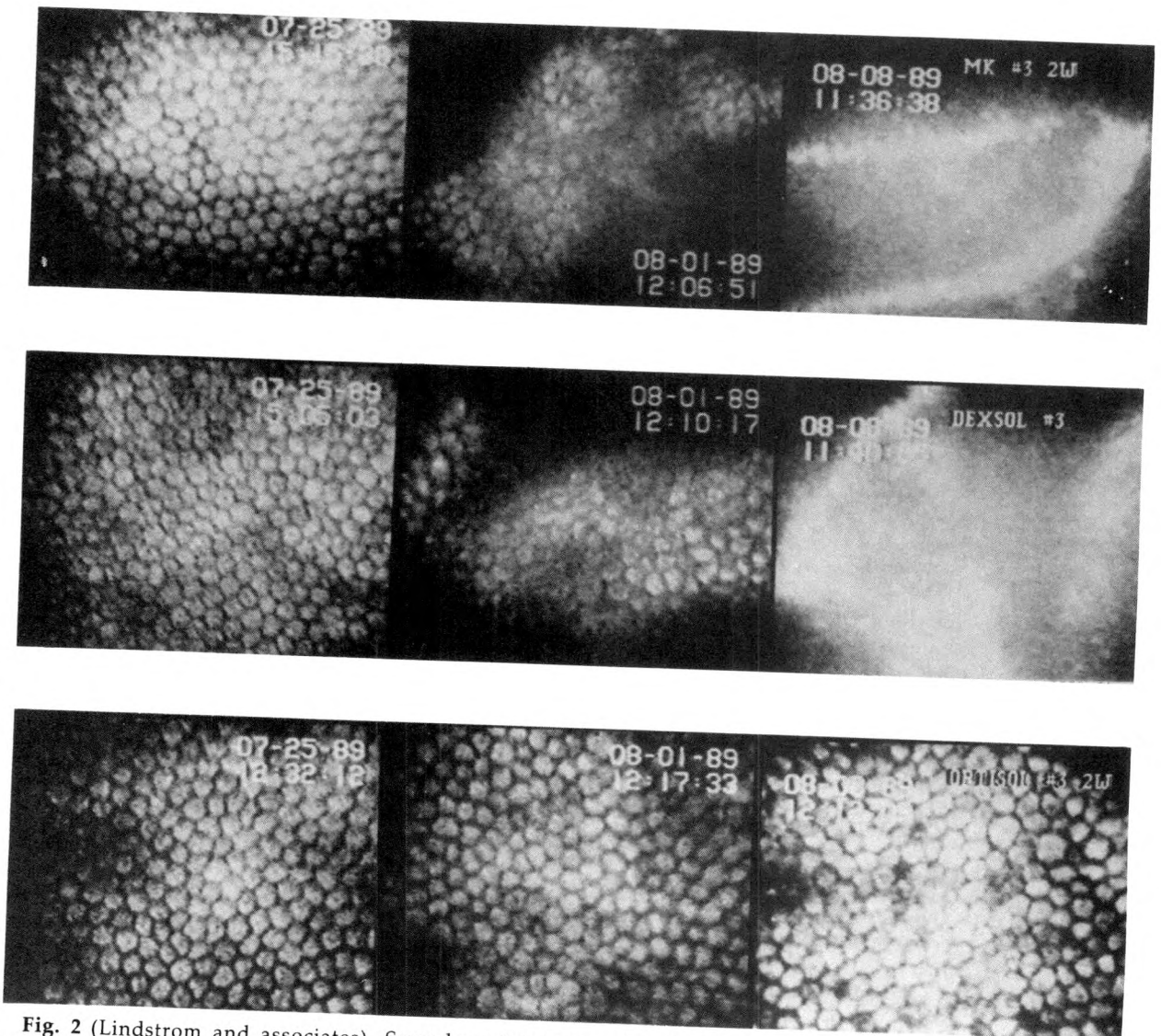


Fig. 2 (Lindstrom and associates). Specular microscopy of endothelial cell layers from corneas stored in McCarey-Kaufman medium (top row), Dexsol (middle row), and Optisol (bottom row) for 0 days (fresh) (left column), 7 days (middle column), and 14 days (right column). Dark areas indicate degradation of endothelial cells.

Fifty-one patients scheduled for penetrating keratoplasty were enrolled in the clinical study (Table 2). Pseudophakic bullous keratopathy was the most common indication for penetrating keratoplasty (27 patients; 53%), which was accompanied by intraocular lens exchange in 23 patients. Of the 51 patients, 43 completed the six-month study; two patients were eliminated because of expulsive intraoperative hemorrhage, one had primary graft failure, two were unable to return for follow-up examinations, and three died before the sixth postoperative month.

The epithelium was intact in 39 of 51 donor corneas (76%) before placement in Optisol and in 29 of 50 grafts (58%) one day postoperatively. None of the tissue had more than 50% defects before storage; seven of 50 grafts (14%) had 50% to 100% defects one day postoperatively. By seven days postoperatively, the epithelium in 42 of 47 grafts (90%) was either intact (36 of 47 grafts, 77%) or had only small (less than 24%) defects (six of 47 grafts, 13%).

Mean central corneal thickness (± standard deviation) was 0.628 ± 0.052 mm intraoperatively in the subset of 17 patients in whom intraoperative pachymetry was performed. Mean thickness increased to 0.688 ± 0.099 mm

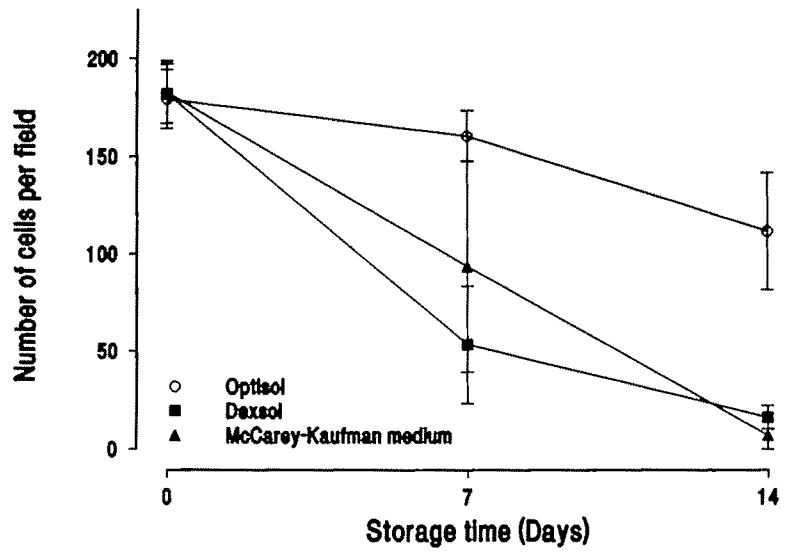


Fig. 3 (Lindstrom and associates). Endothelial cell counts (by specular microscopy) on days 0, 7, and 14 for rabbit corneas stored at 4 C in Optisol, Dexsol, or McCarey-Kaufman medium. Each point represents the mean ± standard deviation of four corneas.

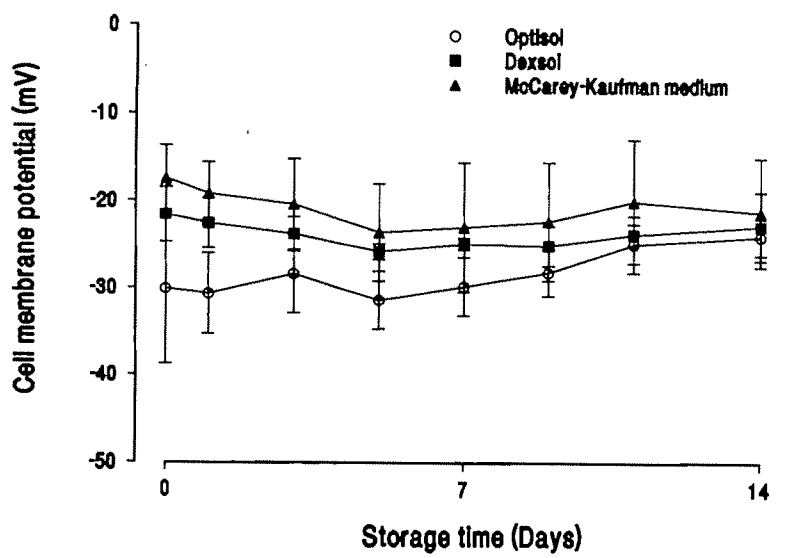


Fig. 4 (Lindstrom and associates). Cell membrane potential for endothelial cells of rabbit corneas stored at 4 C for 14 days in Optisol, Dexsol, or McCarey-Kaufman medium. Measurements were made after corneas were warmed to 24 C for 30 minutes. Cell membrane potential is an index of the efficiency with which the cell regulates the movement of ions and other molecules through its membrane. Each point represents the mean ± standard deviation of four corneas.

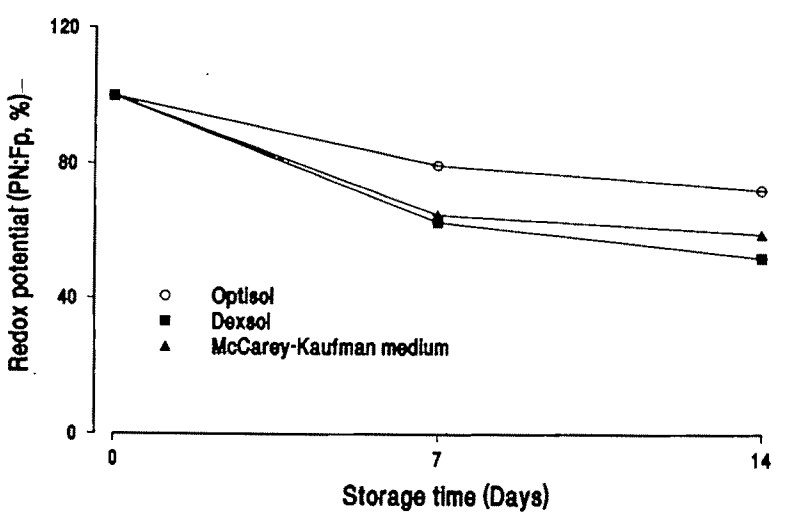


Fig. 5 (Lindstrom and associates). Redox potential measurements on days 0, 7, and 14 for rabbit corneas stored at 4 C for 14 days in Optisol, Dexsol, or McCarey-Kaufman medium. The redox potential is an index of cellular metabolic equilibrium and is expressed in terms of a ratio between two classes of autofluorescent, metabolically active molecules—reduced pyridine nucleotides (PN) and oxidized flavoproteins (Fp). The values are plotted as percentages of the ratio on day 0, which is designated as 100%. Data were insufficient to permit statistical analysis.

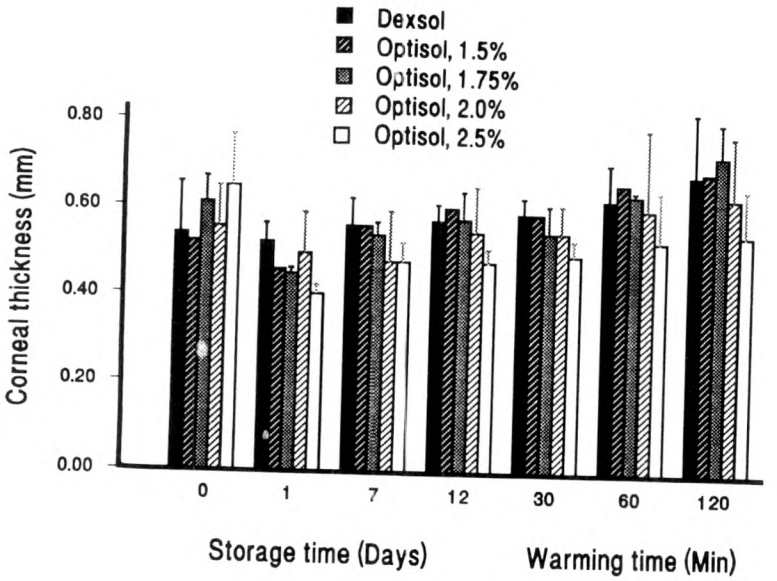


Fig. 6 (Lindstrom and associates). Corneal thickness (measured by micrometer on an upright microscope stage) of human donor tissue stored in Dexsol or in Optisol that contained varying percentages of chondroitin sulfate. The tissue was stored at 4 C and the thickness was measured on days 0, 1, 7, and 12. On day 12, the tissue was warmed to 34 C and the thickness was measured at 30, 60, and 120 minutes. Each bar represents the mean ± standard deviation of three central measurements for all tissue in a given medium at a given time.

one day postoperatively (45 patients), decreased to the intraoperative level by day 7 (42 patients), and continued to decrease thereafter (Table 3).

Mean endothelial cell density decreased 5.0% ± 18.4% (± standard deviation) by three months postoperatively (36 patients) and 11.5% ± 14.4% by six months postoperatively (38 patients), compared to donor corneal endothelial cell densities. There was a slightly positive, but not statistically significant, association between the length of Optisol storage and cell loss at both three and six months (r = .12 and .07; P = .57 and .76, respectively).

Grafts were clear in 41 of 44 patients (93%) examined three months postoperatively; one patient had mild stromal haze, one had fine nebular particles in the graft, and one had a persistent epithelial defect. The patient with the epithelial defect withdrew from the study at three months because of an inoperable choroidal hemorrhage and total retinal detachment. Of the 43 patients examined at the final six-month examination, all but one had clear grafts (42 of 43 patients, 98%). The one patient with a hazy cornea at six months had had a clear graft at three months; this patient required repeated penetrating keratoplasty shortly after this six-month study.

Discussion

This study was divided into the following three phases: in vitro evaluation of endothelial preservation, in terms of metabolic activity and structure, as well as measurement of corneal thickness after varying periods of storage; in vivo examination of epithelial toxicity and inflammation in rabbit eyes; and clinical use in 51 patients who underwent penetrating keratoplasty.

In the first phase, tissue-cultured human corneal endothelial cells incubated at 35.5 C in Optisol incorporated significantly more tritiated thymidine than cells in Dexsol; the presence of adenosine was shown to be the constituent

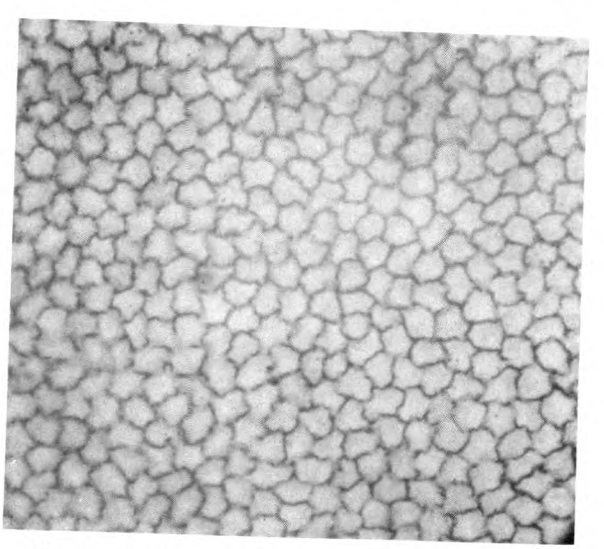


Fig. 7 (Lindstrom and associates). Light microscopic view of human corneal endothelial cell layer stained with alizarin red S after 12 days of storage in Optisol that contained 2.5% chondroitin sulfate (× 250).

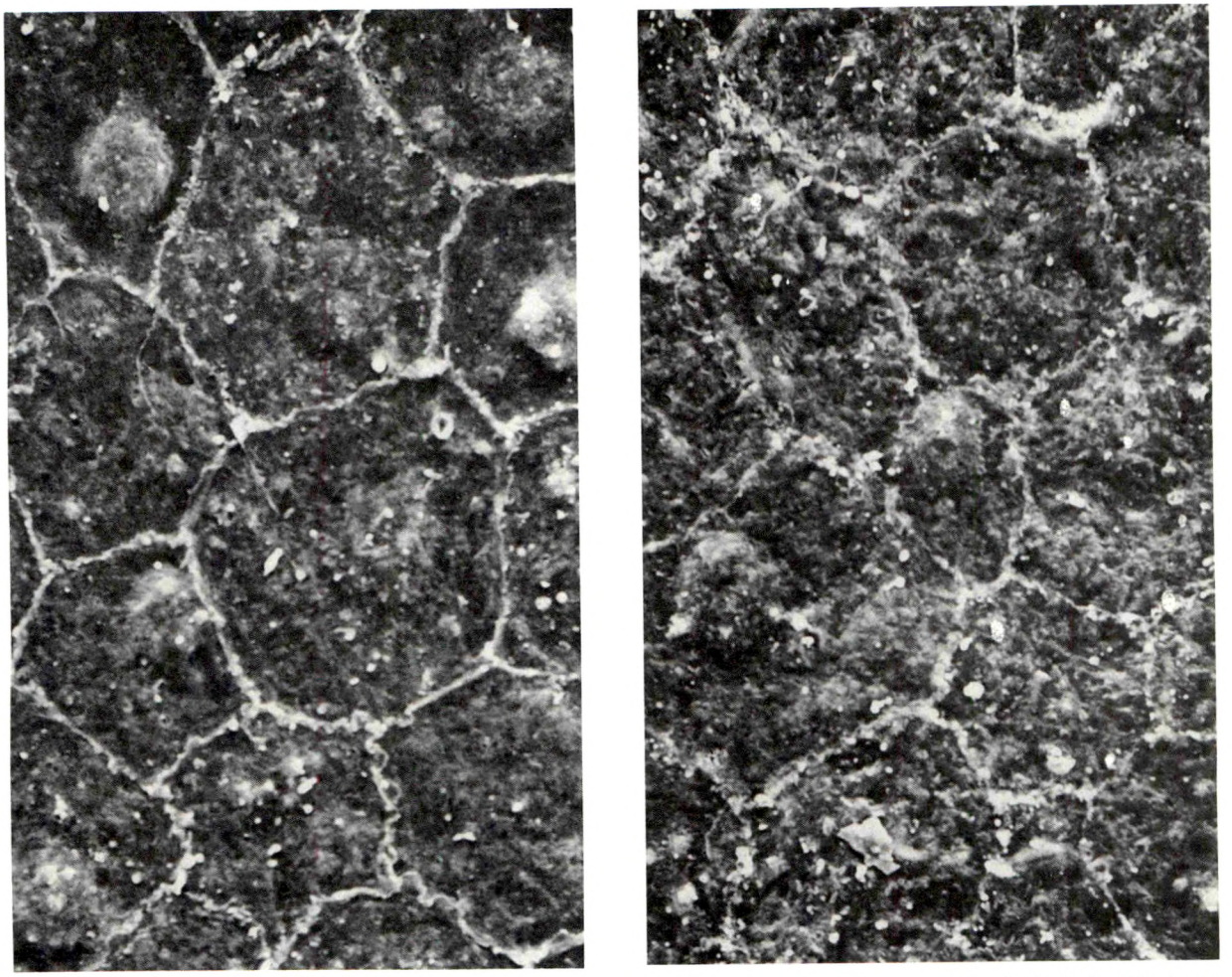


Fig. 8 (Lindstrom and associates). Scanning electron microscopy of human corneal endothelial cells from paired donor corneas after five days of storage at 4 C in Optisol (left) or Dexsol (right). Donor age was 25 years. The cell borders of the Optisol-stored tissue are more intact and distinct, compared to the Dexsol-stored tissue (× 1,870).

responsible for the increased mitotic activity. Although the data suggest increased nucleic acid turnover under these experimental conditions, increases in endothelial cell proliferation may not occur in intact corneas stored in Optisol at 4 C or in situ at physiologic temperatures after penetrating keratoplasty. This bioassay does, however, indicate the absence of cytotoxicity and demonstrates enhanced cellular function apparently related to the addition of precursors (adenosine, inosine, and adenine) for the synthesis of adenosine triphosphate.

In the metabolic studies, measurement of membrane potential in corneal endothelial cells at room temperature (24 C) was used to evaluate changes in penetrability across the endothelial cell layer, as an indication of endothelial cell membrane breakdown over time. The potentials at this temperature were different from those that would be expected at higher temperatures, as has been shown by others with somewhat different methodology.[18] Nevertheless, our results show that the potential difference remained relatively stable over the 14-day storage period in all media (Fig. 4). Although the mean endothelial cell membrane potentials for tissue stored in Optisol, Dexsol, and McCarey-Kaufman medium were different before storage, the data suggest that there are no obvious relationships between lower initial potential and duration of viability of cells in storage. Similarly, determination of the ratio of autofluorescence of reduced pyridine nucleotides to that of oxidized flavoproteins (PN:Fp) showed metabolic stability in the endothelial cells of tissues stored in all three media, with a

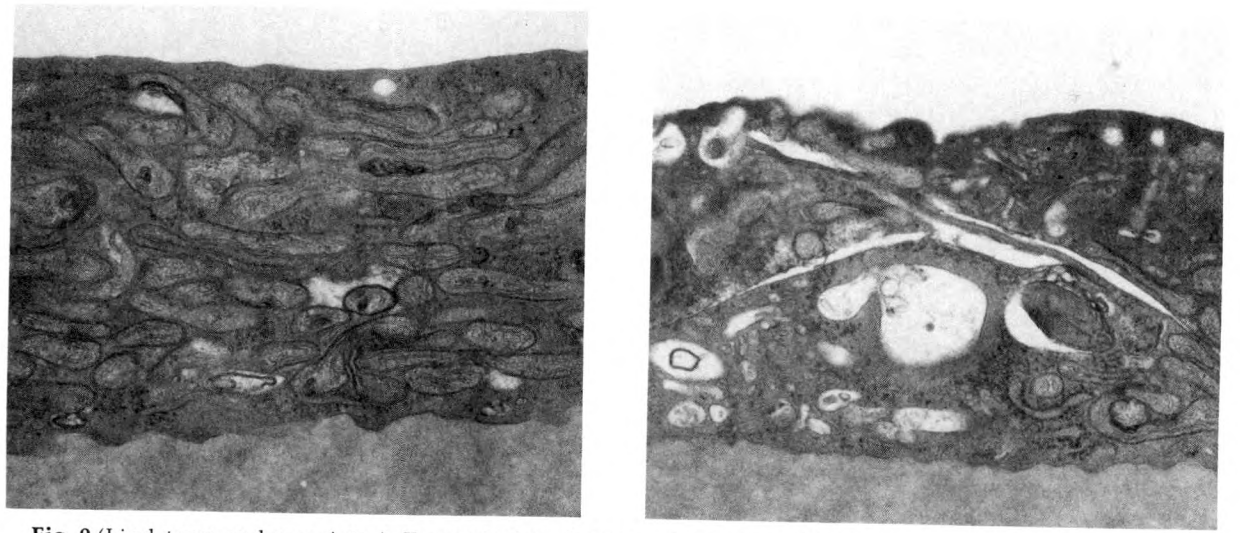


Fig. 9 (Lindstrom and associates). Transmission electron microscopy of human corneal endothelial cells from paired donor corneas after five days of storage at 4 C in Optisol (left) or Dexsol (right). Donor age was 25 years. Both the apical and basal surfaces of the Dexsol-stored tissue are more undulating and irregular than the surfaces of the Optisol-stored tissue (× 26,730).

somewhat lesser decrease in Optisol-stored corneas (Fig. 5).

Although the metabolic studies indicated endothelial cell stability, the structural studies disclosed changes in the endothelial cells of tissue stored in all of the tested media. By specular microscopy, the structure of the endothelium could be seen to change with increasing storage time, such that some of the endothelial cells lost their normally smooth and organized posterior surface and visible cell borders. The result was that areas of the endothelium appeared dark, with no visible intact cells, indicating abnormalities such as structural disorganization and the presence of folds in Descemet's membrane (Fig. 2). However, rabbit corneas stored in Optisol showed more visible endothelial cells per field (Fig. 3), compared to corneas stored in the other two media, which indicated less damage over time in storage. Similarly, electron microscopy of rabbit corneas showed more normal-appearing endothelial cells in the Optisol-stored corneas.

In human corneas from older donors stored in Dexsol or Optisol with varying amounts of chondroitin sulfate, neither trypan blue nor alizarin red S staining (Fig. 7) disclosed any qualitative differences in endothelial cell layer structure or integrity. Scanning and transmission electron microscopy of paired human corneas from donors ranging in age from 22 to 85 years, however, indicated that Optisol that contained 2.5% chondroitin sulfate preserved en-

TABLE 2
CHARACTERISTICS OF 51 PATIENTS ENROLLED IN OPEN-LABEL TRIAL OF OPTISOL-STORED CORNEAL TISSUE

CHARACTERISTIC	NO. (%)
Age (years, mean ± standard deviation)	68 ± 16
Gender	
Men	16 (31)
Women	35 (69)
Indication for surgical procedure	
Pseudophakic bullous keratopathy	27 (53)
Fuchs' corneal dystrophy	9 (18)
Keratoconus	9 (18)
Aphakic bullous keratopathy	3 (6)
Avascular failed graft	1 (2)
Other*	2 (4)
Surgical procedure	
Penetrating keratoplasty and intraocular lens exchange	23 (45)
Penetrating keratoplasty	16 (31)
Penetrating keratoplasty, extracapsular cataract extraction, and intraocular lens insertion	8 (16)
Penetrating keratoplasty and intraocular lens removal	2 (4)
Penetrating keratoplasty and extracapsular cataract extraction	1 (2)
Penetrating keratoplasty and intraocular lens insertion	1 (2)

*Includes one patient with corneal leukoma and another with a corneal scar and irregular astigmatism.

TABLE 3
CORNEAL THICKNESS INTRAOPERATIVELY AND POSTOPERATIVELY IN PATIENTS RECEIVING OPTISOL-STORED CORNEAL TISSUE

TIME	NO. OF PATIENTS	THICKNESS (MM) MEAN ± STANDARD DEVIATION	THICKNESS (MM) RANGE
At surgery	17	0.63 ± 0.05	0.56–0.73
Days after surgery			
1	45	0.69 ± 0.10	0.51–1.06
7	42	0.63 ± 0.09	0.44–0.82
90	39	0.54 ± 0.06	0.40–0.64
180	41	0.54 ± 0.06	0.38–0.70

dothelial structure, in terms of cell borders, cell shape, and endothelial cell layer integrity, better than Dexsol (Fig. 8); changes seen in Dexsol-stored corneas at three, five, and seven days were not seen in Optisol-stored tissue until several days later.

Measurement of corneal thickness showed that 2.5% Optisol-stored tissue was thinner after 12 to 14 days of storage, compared to tissue stored in Dexsol, McCarey-Kaufman medium, or Optisol with reduced amounts of chondroitin sulfate. At all times over the 14-day study, rabbit tissue stored at 4 C in Optisol was thinner than tissue stored in Dexsol or McCarey-Kaufman medium (Fig. 1). Human donor tissue stored in Optisol that contained 2.5% chondroitin sulfate was thinnest at the end of storage and at the end of the warming period (Fig. 6), compared to tissue stored in Dexsol (1.35% chondroitin sulfate) or other formulations of Optisol that contained 1.5%, 1.75%, or 2.0% chondroitin sulfate.

The second phase of these studies demonstrated the safety of Optisol in vivo in rabbit eyes. Optisol was nontoxic to the epithelial cell layer after 14 days of topical application. Histologic examination of these eyes showed no evidence of inflammation.

The open-label clinical study was the final phase of this series. Although interpretation of the clinical findings is limited by the absence of a control group, the results appear to be comparable to those in previously published reports that describe clinical studies of penetrating keratoplasty with tissue stored in other short-term and intermediate-term storage media. The percentage of clear grafts at three months (93%, 41 of 44 grafts) and at six months (98%, 42 of 43 grafts) and the endothelial cell loss at three months (5.0%) and at six months (11.5%) are well within the range of 84% to 100% clarity[2-5,13,15] and 6% to 18% endothelial cell loss[9,10,13,15] observed at similar intervals for tissue stored in McCarey-Kaufman medium, K-Sol, Chondroitin Sulfate Corneal Storage Medium, or Dexsol. The mean thickness of the grafts in this study returned to physiologic levels[19] by 90 days postoperatively as was also found in earlier studies of various storage media.[9,13,15]

Overall, the results of our study suggest that the main advantage of Optisol storage is thinner tissue at the time of the surgical procedure. The mechanism that results in thinner tissue after Optisol storage is not known; it may be related to enhanced endothelial cell function or to the osmotic effect of the higher concentration of chondroitin sulfate in Optisol, compared to Dexsol, which has only 1.35% chondroitin sulfate. Thinner tissue at the time of the surgical procedure permits better evaluation, easier manipulation, and the potential for earlier visual rehabilitation. Postoperative swelling of tissue after transplantation has been observed to result in a wide range of corneal thicknesses one day postoperatively, regardless of the storage medium in which the grafted tissue was stored; the cause of this swelling may be related to an influx of water resulting from the presence of chondroitin sulfate or dextran, or both, in the stroma of the graft,[20,21] but the precise mechanism is unknown and needs further investigation. Nevertheless, the collective results of this study and similar results of other recent studies[22] suggest that corneal tissue can be effectively maintained in this new dextran-chondroitin sulfate–containing medium. Further studies will be required, however, to determine the maximum length of time a cornea can be stored in Optisol and still be transplanted successfully, and to assess whether the formulation of Optisol is more effective in preserving endothelial viability than other corneal storage media currently in use.

ACKNOWLEDGMENTS

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PERSPECTIVES

The Development of New Drugs for Ophthalmology

Gary D. Novack, Ph.D.

Drug development is a special application of the scientific method. In the scientific method, one generates a testable hypothesis, conducts an experiment, and then either rejects or fails to reject the hypothesis. One then conducts additional experiments on the basis of the outcome of the first experiment. The key feature of the scientific method is a testable hypothesis. If there is no hypothesis (that is, only data gathering), or the hypothesis is not testable, then it is not considered scientific research. In drug development, the testable hypotheses relate to the efficacy and safety of the drug.

The time and expense involved in developing new drugs is substantial. Accounting for the cost of research and development on a product basis is complex. It is difficult to assign costs to basic research (for example, how does the ciliary body produce aqueous humor) vs specific drugs (for example, evaluating Drug A as a suppressor of aqueous production).[1] The considerable task of estimating these costs was undertaken by DiMasi and associates.[2] Working with confidential data supplied by pharmaceutical firms for all medical specialties, they calculated that the interval and cost involved from chemical synthesis to marketing approval (Figure) average 12 years and $114 million (1987 dollars), respectively. Capitalizing this out-of-pocket expense to the point of marketing approval at a 9% discount rate yields an average cost estimate of $231 million.[2] Unfortunately, it is not possible at this time to gather from their data development costs and timing for the subset of ophthalmic drugs.

Many drugs used in ophthalmology were originally developed for the treatment of systemic disease, with their ophthalmic uses being found subsequently. To decrease business risks and development time, some ophthalmic pharmaceutical companies have licensed from another company the ophthalmic rights to their systemic drugs. Examples include ciprofloxacin, flurbiprofen, levobunolol, metipranolol, and fluorometholone. Although systemic development of these drugs was probably near the estimate provided by DiMasi and associates,[2] the incremental cost of ophthalmic development was probably much less. As more drugs are targeted for ophthalmic use first, rather than for systemic use, costs of development are no longer incremental, but approach the large sums discussed for systemic drugs. Examples of these drugs used for ophthalmic indications first, rather than later, include the topical carbonic anhydrase inhibitors and anticataract drugs.

Drug development is usually sponsored by for-profit pharmaceutical firms. While there is

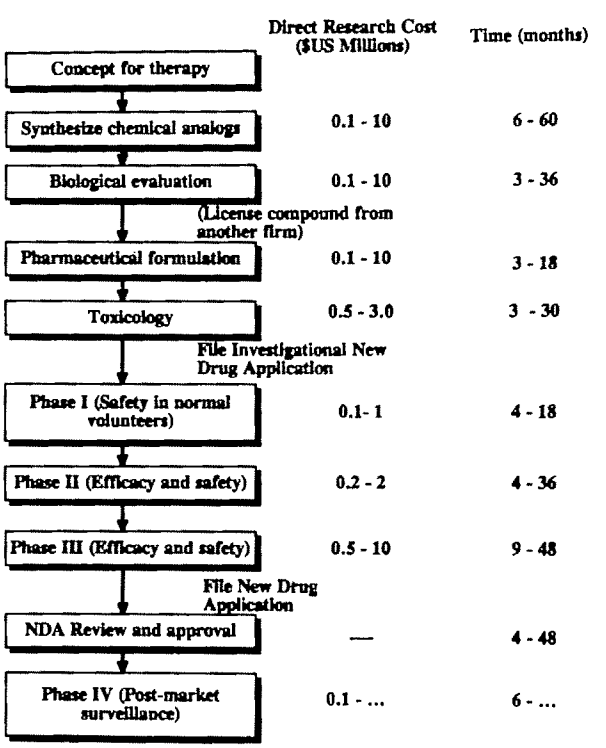


Figure (Novack). The drug development process. Timing and direct research cost is provided on the basis of my experience. Additional developmental costs, not displayed, may include chemistry and manufacturing expenses, capital equipment and facilities, administrative and management time, insurance, and the cost of funds. Ellipses indicate no upper limit.

an opportunity for profit for the investors, there is also a great risk. Approximately 99.9% of compounds synthesized do not become revenue-producing products for the company because of inadequate efficacy, unacceptable toxicity, or other reasons. The key in the scientific method of drug development is to ask the question (that is, experiment early in the development process), before resources are expended unnecessarily. For example, if the goal is to develop a longer-acting pilocarpine, then the duration of the ocular hypotensive action of the new agent relative to that of conventional pilocarpine is the most important experiment. If a more comfortable anti-inflammatory agent is the goal, then an early experiment should compare the new agent to a currently marketed one.

Discovery and development of drugs is a sequential process (Figure). A new therapeutic agent frequently begins as a theoretical modification of a physiologic process. Examples include the antagonism of the chronotropic effects of catecholamines (propranolol),[3] or antagonism of carbonic anhydrase in the ciliary body (acetazolamide).[4] In such cases, the body's own agonist or enzyme substrate is the chemical starting point for a series of analogues (Figure).

Various chemical analogues are next synthesized, and evaluated in in vitro and in vivo models for this disease. The biologic model need not be an exact model of the disease, but merely a model for the disease. That is, the model's sensitivity and specificity with respect to existing clinical therapies is more important than whether the animal disease is actually similar to the human disease.[5] For example, β-adrenoceptor antagonists, although not very effective as ocular hypotensive agents in normal rabbits, can antagonize the ocular hypotensive effects of isoproterenol. This action of the β-adrenoceptor antagonist, which is actually a hypertensive effect, can be used to evaluate new agents for intraocular β-adrenoceptor blockade in a relatively inexpensive model.[6]

The next step is pharmaceutical formulation, which begins with an evaluation of the molecule's stability and solubility. An ideal drug candidate has the optimal physicochemical properties to enable it to cross the corneal barrier readily. The most preferred delivery system for ophthalmic agents is an aqueous eyedrop. A drug may be insoluble in water, necessitating a micronized suspension. Thus, pharmaceutical scientists are challenged to develop aqueous formulations in which the drug remains stable for a product shelf life of at least two years at controlled room temperature (15 to 30 C). Multidose containers require protection against microbial contamination; thus, a preservative that is compatible with the drug and not irritating to the eye must be added. The pH and buffering of the formulation must not lead to discomfort, and the viscosity must not interfere with instillation or visual transparency. Some drugs are inherently discomforting, and acceptance can be provided only by decreasing the concentration of the active molecule in the final formulation.

The next step in drug development is toxicology. Also known as safety evaluation, this step involves exposing several species of animals to increasingly larger doses and durations of treatment with the test compound. This continuum begins with short-term studies (one dose up to several instillations per day), continues with intermediate-term studies (up to one month), and finally long-term studies (six to 12 months). These studies evaluate any changes in animal health or behavior, as well as extensive gross and microscopic pathologic characteristics. Acute and subacute studies are generally required before testing of the new drug in humans. The commitment of resources for long-term studies is generally not made until there are some positive data from the short-term human trials. Drugs intended for long-term use also may require in vitro evaluation of their mutagenicity, and in vivo evaluation of their potential for eliciting birth defects (teratogenicity) and cancer (carcinogenicity).

At this point, the company evaluates the biologic evidence for activity, its potency for efficacy relative to its potency for toxicity, and the suitability of the compound for acceptable formulations. If these criteria are met, and there still is a large projected therapeutic need for this type of compound, then the firm proposes clinical evaluation. A regulatory submission is required in most countries to administer an investigational drug to humans. In the United States, this regulatory submission is called an Investigational New Drug Application. This submission includes reports from the biologic, toxicologic, and pharmaceutic studies, the proposed clinical plan and indication for use, and the chemistry and pharmaceutics to demonstrate a stable, known product. In practice, a firm generally confers with the Food and Drug Administration before submitting an Investigational New Drug Application to assure that the early development plan will provide sufficient

data, and be of limited risk to volunteers and patients. Ophthalmic drugs are currently reviewed by the Food and Drug Administration's Division of Medical Imaging, Surgical, and Dental Drug Products. Technically, the Investigational New Drug Application is a notification to the Food and Drug Administration that, if no contrary word is heard, the company will begin the proposed clinical studies in approximately 30 days. The filing of an Investigational New Drug Application, and its status, is confidential, unless released by the firm. Therefore, it is not possible to state accurately the number of drugs under active clinical investigation for ophthalmic indications, or their developmental status.

Clinical research studies are divided into four major phases (Phases I through IV). Phase I studies are intended primarily to evaluate the safety and pharmacokinetics of the new drug in normal volunteers. These studies start with low doses for brief periods of administration (one drop, for example), and continue through more extended concentrations, frequencies, and durations. The objective is to monitor the safety of the product while slowly increasing the exposure (dose, frequency, or duration) to the volunteer. The comfort of the formulation is often assessed at this time.[7-9] I know of several potential products that were found unacceptable at this stage—either because of discomfort of a new vehicle, or discomfort of a combination of two agents that were comfortable given separately, but not together. In the United States today, it is important to know the systemic exposure of ocularly instilled drugs. It is during Phase I that many firms choose to evaluate plasma levels of the topically applied drug.[10] Only approximately one third of all drugs entering Phase I evaluation make it to Phase III evaluation.[2] A drug clears Phase I evaluations with negative data; that is, the absence of notable ocular or systemic toxicity at intended therapeutic doses. The patent position on the proprietary nature of the new drug may not be clear at this time. For these reasons, few Phase I studies are submitted for publication. As toxicology on the drug's potential teratogenicity is generally not complete at this time, the inclusion of women of child-bearing potential in these studies is restricted.

If the drug is indicated for a relatively rare disease (less than 200,000 patients/year, for example), then a firm may consider applying for an orphan designation. Granting of this designation provides tax and marketing exclusivity incentives, as well as the potential for publicity. An orphan drug must still be evaluated in the various phases of clinical investigation, but smaller patient numbers are generally required as, by definition, less patients are available for study.[11]

All clinical evaluations should be conducted by an independent investigator in studies designed to minimize bias. When possible, this involves masking the study medications, and the use of positive and negative controls.[12] For example, if one is evaluating the mydriatic potential of a new drug, one should attempt to include both a mydriatic (cyclopentolate, for example) as a positive control and the vehicle of the new drug as a negative control. When it is difficult to mask the investigator from the treatment (with laser or surgical procedures, for example), one may consider using an independent observer to make critical measurements.[13] Any proprietary relationship of the clinical investigator with the product being evaluated should be disclosed.

Phase II studies also use dosage escalation regimens similar to those of Phase I, but in patients with the intended disease, rather than in normal volunteers. Phase II studies include dose-response, time-response evaluations.[14,15] Early Phase II studies are generally placebo-controlled, as absolute efficacy is the first question.[16,17] If enhanced efficacy or safety over existing therapy is a sine qua non for the putative product, then Phase II studies may incorporate active controls. It is only after the completion of a Phase II trial that the pharmaceutical company gets human efficacy data for their compound. The interval from demonstration of efficacy in animal studies until receipt of results from Phase II studies may be up to several years, and cost several million dollars. First results of efficacy studies in the medical literature or at meetings are usually based on a pilot Phase II study. Examples of ophthalmic drugs for which further development was stopped after Phase II include metoprolol (too short acting)[18] and di-acetyl-nadolol (blepharoconjunctivitis).[19]

Once there is demonstration of efficacy in patients, there are many ethical, financial, scientific, and political pressures to proceed rapidly toward the next step, Phase III trials. However, investigation as to the selection of the appropriate concentration and frequency of use should be a key segment of Phase II investigations. Many clinical pharmacologists in industry, government, and academia believe that in

hastening Phase III trials, one fails to optimize the dose. With oral therapy in systemic medicine, the dose may be modified by administering two pills rather than one or by cutting a pill in half. In ophthalmology, a dose cannot realistically be modified by instilling a second drop, or instilling one half of a drop. Many of our marketed drugs are available in only one or two concentrations, so that only the frequency of use can be modified. If only one concentration can be selected for further development, a higher concentration is usually favored over a lower concentration to maximize efficacy, although there might be greater potential safety with the lower concentration. This tendency to select dosing that represents the "plateau" phase of the dose-response curve is probably reasonable for drugs with large therapeutic indices (for example, antibiotics), but probably worthy of further exploration for drugs with narrower therapeutic indices (for example, autonomic drugs and corticosteroids).

Phase III studies are extended trials (up to one year of dosing per patient) in large patient populations (generally 100 to 1,000) that use the concentration, formulation, and dosing regimens of the intended marketed product.[20-23] Both safety and efficacy are measured in Phase III. For most drugs, at least two Phase III trials are required to provide substantive evidence of efficacy and safety. As with all clinical trials, the cost of Phase III trials includes the physician's time for examining and treating the patient, laboratory tests, inpatient stays, the study medications, and study management and data handling. As at least two Phase III trials must be conducted that must include large numbers of patients for long treatment periods, this is the most expensive phase of drug development, with costs ranging from hundreds of thousands to millions of dollars. The logistics of administering these large studies often exceed the ability of the pharmaceutical company's staff, and so independent private research organizations sometimes are employed to assist in the trial management. An example of an ophthalmic drug rejected after Phase III trials is oral sorbinil for diabetic retinopathy, which was rejected because of inadequate efficacy.[24]

An important definition in comparative trials of efficacy and safety is the clinically significant difference. Any measurement in a patient is confounded by inherent variability among patients, the pathologic condition, drug manufacture, compliance, and the measurement error of any device used. One must define what change, if observed consistently, would constitute a meaningful difference. Both the firm that designs the studies and the Food and Drug Administration reviewers must agree on the dividing line for differences that are meaningful. For the recently approved ophthalmic quinolone antibiotics, a clinically significant difference was a 20% difference in cure rates between the quinolone and the standard therapy (tobramycin or gentamicin). This required approximately 80 to 100 patients who met all protocol requirements per treatment group. However, because only 42% of patients who entered with clinical bacterial infections met the rigorous culture requirements,[22] approximately 450 patients per trial, or 900 Phase III patients were required. For a recently approved topical anti-inflammatory drug, a clinically significant difference was 0.5 to 1.0 grades in anterior chamber cells (0 to 3 scale). This required approximately 100 patients per group per study.[25]

Several years ago, some researchers had proposed a decrease in intraocular pressure of 4 mm Hg as a clinically significant difference in ocular hypotensive therapies. This means that the difference in reducing intraocular pressure between the two drugs would be, at most, 4 mm Hg. From today's perspective, that difference was too liberal, as the ocular hypotensive efficacy of several agents was found equivalent to that of timolol within 4 mm Hg, but not within 2 mm Hg. For recently approved ocular hypotensive agents, a clinically significant difference was judged as 2 mm Hg.[7] This required approximately 30 to 50 patients per group per trial. An even more rigorous standard, such as 1 mm Hg, is debatable. At this time, I know of no agent with an ocular hypotensive efficacy that would be found equivalent within 2 mm Hg, but not within 1 mm Hg. A clinician probably would not judge two agents that differed by only 1 mm Hg in their ocular hypotensive efficacy to be clinically different. If this more rigorous standard was selected, it would require a doubling of the sample size (and therefore costs and time) to reach this standard. Equivalency standards can also be set for safety measures. However, even with the dimensions of Phase III trials, only relatively frequent adverse experiences (that is, incidence of 1% or greater) are expected to be detected, and differences in safety between agents are difficult to detect.

In designing a Phase III trial, the standards for regulatory review several years in the future

must be predicted. For example, antiglaucoma drugs have been approved to date on the basis of their ocular hypotensive efficacy. Increased intraocular pressure carries with it an increased risk of further progressive loss of visual field.[26,27] Also monitored in studies for approved drugs were visual field (either by manual Goldmann or automated threshold techniques) and cup/disk ratio (by direct ophthalmoscopy). There is a large peer-reviewed literature on the influence of accepted glaucoma therapies on these measures. We know what the standard therapies do to these measures, and how to interpret statistically significant differences vis-a-vis their clinical relevance.[28] There are many developing procedures for the measurement of ocular disease, including new visual field tests,[29,30] stereoacuity,[31] retinal nerve fiber layer photography,[32,33] and measures of color vision function.[31,34,35] In the future, these measures of visual function may become standards of care in evaluating the effect of glaucoma therapy. However, to my knowledge, such tests are not yet fully validated as to their ability to measure the efficacy of glaucoma therapy. Validation would come from controlled clinical trials as well as clinical experience in how meaningful such measures are in diagnosis and therapy. One would hesitate to risk the time and resources of a Phase III trial that uses investigational measurement systems to evaluate investigational agents.

Another decision in study design is the crossover vs parallel comparison. In a crossover study, each patient receives each treatment in a separate period. In a parallel study, patients are randomly assigned to receive only one of the treatments. Crossover studies require fewer patients than parallel studies, and have the inherent appeal of using each patient as their own control. However, in a crossover study, all patients have to complete all periods, there can be no unequal carryover of treatment effect from one period to the next, and the disease must remain stable.[36] Because β-adrenoceptor antagonists have effects for at least two weeks,[37] a crossover trial is probably not the best study design for evaluating these types of agents.

Patients generally underdose both in number of doses and in interval between doses.[38,39] This would tend to underestimate both efficacy and toxicity of a drug, and complicate the evaluation of a new therapy. An objective measure of compliance would be preferred so that the relationship of lack of efficacy or side effects to underdosing or overdosing could be analyzed. Although there are commercially available devices to monitor compliance with oral medication regimens,[40] none is currently available for ophthalmic medication.

If the agent proves effective, relatively safe, and has the intended characteristics (safer than current therapy, or greater efficacy or longer duration of action, for example), then the firm requests marketing approval from the Food and Drug Administration. This request, called a New Drug Application in the United States, is a large submission (up to 150 volumes) that requires the integration of the extensive clinical program (which may involve millions of pieces of data). Each piece of clinical data must have been checked from its source (generally a case report form) through its various electronic manipulations. A minimum of several months are involved in this data quality check and the subsequent rigorous statistical analysis. The New Drug Application must include the toxicology, chemistry, manufacturing, and controls data. The firm must have demonstrated that the product can be manufactured at a site that meets the rigorous demands of quality control and repeatability.

As mentioned previously, many drugs have already been approved for systemic use before the submission of the New Drug Application for the ophthalmic indication (norfloxacin, for example). The experience with the systemic use of the drug provides a larger knowledge base for the Food and Drug Administration in their review of the possible risks associated with the drug. The review of New Drug Applications for all specialties by the Food and Drug Administration averages from one to three years over the past three decades.[41] There are examples of short review times in ophthalmology (apraclonidine was reviewed in less than three months, for example). However, the review time for most recently approved ophthalmic drugs falls into the previously mentioned range. The review is generally an interactive process, in which the Food and Drug Administration may ask for clarification, reanalysis, additional studies, or revisions to the proposed indications. On approval of the New Drug Application, the company may sell the drug as prescribed by physicians.

Not all ophthalmic drugs and their indications have approved New Drug Applications at the Food and Drug Administration. Drugs introduced before 1962 such as pilocarpine, epinephrine, or oral fluorescein are not approved, but their use is acceptable in standard practice.

Still other drugs are approved for one indication, but prescribed for another. For example, as yet, no topical noncorticosteroidal anti-inflammatory drug is approved in the United States for the treatment of cystoid macular edema. These agents may be prescribed for this indication by an ophthalmologist, but a firm may not promote their drug for this unapproved claim. Recently, the Food and Drug Administration has taken a strong line against promotion for unapproved indications.

Phase IV studies are conducted either during the review period, or after approval. These studies may be for extended indications[42] (additional dosage regimens or diseases, for example), or extended human experience for safety evaluation in larger patient populations in more realistic use (postmarket surveillance, for example).[43-45] In this phase, the use of one agent when used in combination with another marketed product may be further evaluated. In my experience in this area, the initial New Drug Application for levobunolol was for the 0.5%-strength formulation for once- and twice-daily use, with both placebo- and timolol-controlled studies. During the approximately two-year review period, and in the ensuing years, Phase IV studies were conducted on the use of the 0.25%-strength formulation of levobunolol, with both once- and twice-daily administration, for intraocular pressure increases after laser or cataract surgical procedures, and in comparison to other marketed agents such as betaxolol and metipranolol.[46-50] Supplements to the New Drug Application have so far resulted in approval for 0.25% levobunolol with a twice-daily administration.

Many of our new therapies in ophthalmology will come from the development of compounds as sponsored by private pharmaceutical firms. This process is long, risky, and requires rigorous controls in scientific procedures, interpretation, and quality control. This overview of the drug development process emphasized the clinical investigation phases. With the synergistic cooperation of basic and clinical scientists, clinical investigators, and our colleagues in pharmaceutics and regulatory affairs, we can continue to provide new therapies for patients.

From Pharma•Logic Development, Inc., and University of California, Irvine, California. This study was presented in part at the combined American Glaucoma Society/Annual North American Glaucomatologists Learning Ensemble meeting in Coronado, California, Dec. 14, 1991.

Reprint requests to Gary D. Novack, Ph.D., Pharma•Logic Development, Inc., 46 Ashwood, Irvine, CA 92714.

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LETTERS TO THE JOURNAL

Total Detachment of Descemet's Membrane After Small-incision Cataract Extraction

Marian S. Macsai, M.D.

Department of Ophthalmology, West Virginia University Health Sciences Center.

Inquiries to Marian S. Macsai, M.D., Department of Ophthalmology, West Virginia University Health Sciences Center, Morgantown, WV 26506.

Small-incision cataract extraction has provided rapid visual rehabilitation for many cataract patients through the use of a small incision. I encountered a case of total detachment of Descemet's membrane that did not respond to conservative management, or surgical repositioning after small incision cataract extraction. Penetrating keratoplasty was necessary for visual rehabilitation.

A 79-year-old woman underwent uncomplicated small-incision cataract extraction under local anesthesia. A 4-mm scleral tunnel incision was made 2 mm posterior to the surgical corneoscleral limbus with an internal corneal lip incision. The anterior chamber was filled with sodium hyaluronate. A 360-degree continuous tear capsulotomy was performed, and the lens was removed with phacoemulsification, followed by mechanical irrigation and aspiration. The capsule was then reformed with sodium hyaluronate, and a foldable intraocular lens was introduced into the capsule with an injector delivery device. The sodium hyaluronate was removed, and the wound closed with a single 10-0 nylon suture.

On the first postoperative day the wound was tight but a total detachment of Descemet's membrane was noted. Air was injected into the anterior chamber to reposition Descemet's membrane, and the patient recovered visual acuity of 20/40. On the fourth postoperative day, Descemet's membrane was again totally detached. Repositioning was accomplished with sodium hyaluronate, and Descemet's membrane was sutured into position with 10-0 polypropylene. Despite surgical reattachment of Descemet's membrane, the patient's corneal stroma remained edematous over the next two months and epithelial bullae formed. Two months after the initial procedure, the patient was referred and underwent an 8.0-mm penetrating keratoplasty. After removal of the corneal button, Descemet's membrane easily separated from the posterior stroma. Descemet's membrane was repositioned in the corneal periphery with sodium hyaluronate, and an 8.25-mm donor cornea was sutured into position with 12 interrupted full-thickness corneal sutures. The sutures were placed full thickness in order to reposition the host Descemet's membrane. A 12 bite 10-0 nylon continuous suture was then placed. On the first postoperative day the host Descemet's membrane was repositioned. Six months postoperatively the patient had recovered visual acuity in the right eye of

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Letters must be typewritten, double-spaced, on 8 1/2 x 11-inch bond paper with 1 1/2-inch margins on all four sides. (See Instructions to Authors.) An original and **two** copies of the typescript and figures must be sent. The letters should not exceed 500 words of text. A maximum of two black-and-white figures may be used; they should be cropped or reducible to a width of 3 inches (one column). Color figures cannot be used. References should be limited to five.

Letters may be referred to outside editorial referees for evaluation or may be reviewed by members of the Editorial Board. All letters are published promptly after acceptance. Authors do not receive galley proofs but if the editorial changes are extensive, the corrected typescript is submitted to them for approval.

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20/25 with a manifest refraction of +1.50 +2.50 × 45 degrees.

Descemet's membrane detachment is a well-described, unusual complication of cataract extraction.[1-3] Previously described maneuvers[4,5] to hasten the reattachment of Descemet's membrane were unsuccessful in this case. The extensive corneal edema that persisted after sutures were used to reappose Descemet's membrane prompted surgical intervention with penetrating keratoplasty.

The exact mechanism of detachment of Descemet's membrane in this case is unclear. The advent of small incision cataract surgery has allowed for rapid visual rehabilitation in many patients. However, a small incision may predispose the patient to trauma at the edge of Descemet's membrane. The use of a foldable intraocular lens with an injector delivery device may increase the risk of Descemet's detachment from an internal corneal lip incision when there is a snug fit requiring some force on the part of the surgeon to introduce the instrument or the implant into the eye. Many small localized Descemet's detachments will spontaneously reattach. The use of a small incision with an internal corneal lip may make the risk of a localized Descemet's detachment more likely. A slight extension of the interior incision may decrease the incidence of trauma to Descemet's membrane.

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Treatment of Acquired Intermittent Horizontal Jerk Nystagmus With Baclofen

Bruce A. Miller, M.D., Deirdre A. Younger, B.S., and David S. Friendly, M.D.

Department of Ophthalmology, George Washington University Medical Center (B.A.M., D.S.F.); and Children's National Medical Center (D.A.Y., D.S.F.).

Inquiries to Bruce A. Miller, M.D., 3358 Second St. S., Arlington, VA 22204.

A 6-year-old boy had a one-month history of "shaking eyes," according to his mother. The episodes occurred two to three times per day and lasted from seconds to over an hour. There did not seem to be an inciting event and the nystagmus resolved only after rest. Medical history included excision of a posterior fossa ependymoma in 1989 (two years before the onset of nystagmus) followed by adjuvant chemotherapy and radiotherapy. The patient was asymptomatic and tumor-free, as evidenced by recent magnetic resonance imaging scans.

Examination during a recurrence of the nystagmus disclosed a right beating, horizontal jerk nystagmus. A right face turn with left gaze was assumed by the patient to obtain a relative null zone. Binocular visual acuity was 20/40+ while nystagmus was present and 20/25 when it was absent. The direction of beating and the face turn were always the same. When the nystagmus was not present, the eye was normal in all respects.

Because the patient's parents strongly desired a trial of treatment, baclofen[1-3] (which has been successful in the treatment of some forms of acquired nystagmus) was initiated. A total daily dose of 20 mg in four equally divided portions seemed to be best in a preliminary trial. The apparent success prompted a placebo-controlled trial involving 30 days of drug, 30 days of placebo, and appropriate washout periods. The patient's mother kept a detailed log of the number of episodes of nystagmus per day, including the duration and intensity of each episode. All three factors markedly decreased during the baclofen phase of the study when compared to the placebo phase.

Horizontal jerk nystagmus is indicative of a disorder involving the vestibular system, but this particular acquired intermittent, horizon-

tal jerk nystagmus does not fall into a described classification. One condition, benign paroxysmal positional vertigo, can have associated intermittent nystagmus, but vertigo was not a component in our patient.

Baclofen has shown promise in the treatment of acquired periodic alternating nystagmus. This form of spontaneous nystagmus beats in one direction for one to two minutes, followed by a null period, and continuation of nystagmus in the opposite direction for a similar length of time. Baclofen is an analogue of aminobutyric acid. Its mode of action is not fully understood; however, it inhibits monosynaptic and polysynaptic transmission at the spinal level, and also depresses the central nervous system. It is used for the symptomatic relief of muscular spasm caused by conditions such as multiple sclerosis and lesions of the spinal cord.[1-4] Our trial suggests that baclofen may be a useful drug in the treatment of acquired nystagmus other than periodic alternating nystagmus.

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Anaphylactic Shock and Death After Oral Intake of Acetazolamide

Jesús Peralta, M.D., José Abelairas, M.D., and José Fernández-Guardiola, M.D.

Service of Ophthalmology, Hospital La Paz.

Inquiries to Jesús Peralta, M.D., Service of Ophthalmology, Hospital La Paz, 28046, Madrid, Spain.

A 66-year-old woman with chronic open-angle glaucoma was admitted to our service in order to control her intraocular pressure. Topical therapy with timolol maleate and dipivefrin had been insufficient. Oral administration of acetazolamide, 250 mg every six hours, was started. After the first dose the patient developed an anaphylactic shock with associated laryngeal edema and respiratory distress syndrome. Despite intensive care, the patient died. She had been taking no other medication and had no history of allergy or hypersensitivity.

There have been other reports of adverse effects of acetazolamide.[1,2] The reaction in the patient we have described could have been attributable to a sulfonamide hypersensitivity caused by a cross-sensitivity with other drugs of this family, probably those used as bacteriostatics, since these pharmacologic agents were profusely used in our country for decades.

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Lateral Tarsorrhaphy for a Noncompliant Patient With Floppy Eyelid Syndrome

Charles S. Bouchard, M.D.

Department of Ophthalmology, Loyola University Medical Center. Presented at the annual meeting of the Ocular Microbiology and Immunology Group, Anaheim, California, Oct. 12, 1991.

Inquiries to Charles S. Bouchard, M.D., Department of Ophthalmology, Loyola University Medical Center, 2160 S. First Ave., Maywood, IL 60153.

Floppy eyelid syndrome is characterized by a chronic diffuse papillary conjunctivitis, easily everted upper eyelids, and nocturnal eyelid eversion.[1] Typically, overweight young men are affected.

Treatment generally includes an eye shield at bedtime with topical lubricants, corticosteroids, or antibiotics. Horizontal full-thickness

eyelid tightening procedures have also been advocated.[2,3]

A 30-year-old, obese man was initially seen on Feb. 5, 1990, because of redness, tearing, and discharge in his left eye for one year. His visual acuity at that time was R.E.: 20/25 and L.E.: 20/60. The initial diagnosis was bacterial conjunctivitis.

Despite several regimens with topical antibiotics and corticosteroids, the patient's symptoms persisted. On May 29, 1990, a diagnosis of floppy eyelid syndrome was made. The patient was initially treated with eyelid taping at bedtime. A Fox shield at bedtime and later prednisolone acetate and sulfacetamide drops were added to the regimen. His symptoms persisted.

On Dec. 10, 1990, the patient underwent a pentagonal resection of the lateral third of his left upper eyelid. A characteristic chronic inflammatory infiltrate, decreased goblet cells, and keratinized stratified squamous epithelium were present.

On March 19, 1991, the patient developed a superior corneal infiltrate. This was initially treated with polymyxin/trimethoprim drops six times a day. When the infiltrate progressed, he was referred to the Cornea Service.

On initial examination on March 22, 1991, the patient had a 2.7 × 4.0-mm superior paralimbal infiltrate with an overlying epithelial defect (Fig. 1). His persistent eyelid distensibility was also still evident (Fig. 2). His visual acuity in the left eye was 20/200. He also had rosacea. Corneal cultures grew three colonies of coagulase-negative staphylococcal species. One colony was resistant to all the screening antibiotics except vancomycin.

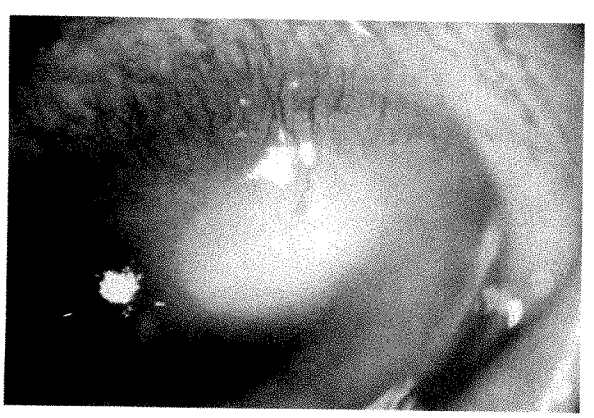


Fig. 1 (Bouchard). A 2.7 × 4.0-mm superior corneal infiltrate with overlying epithelial defect.



Fig. 2 (Bouchard). Persistent eyelid distensibility three months after a pentagonal resection of the lateral third of the left upper eyelid. The superior corneal infiltrate is visible.

Because of suspected noncompliance with the topical medications, the patient was eventually admitted three times between April 3 and May 20, 1991. During his hospitalization, the infiltrate improved with frequent topical 2% vancomycin drops and erythromycin ointment. The infiltrate recurred after each hospital discharge. Doxycycline was prescribed for his rosacea blepharoconjunctivitis.

On May 20, 1991, a lateral tarsorrhaphy was performed. The decision to perform a tarsorrhaphy was made after multiple episodes of finding the patient sleeping on the affected side with his eyelid mechanically opened. His palpebral conjunctiva and globe were in direct contact with the pillow.

The patient was last examined on Nov. 12, 1991. At that time the tarsorrhaphy was in place, and his visual acuity was 20/25−3. His cornea had a superior, white subepithelial and minimally vascularized scar. His tarsal conjunctiva was still rubbery and diffusely mildly injected and smooth. His medications included erythromycin ointment at bedtime and fluorometholone, one drop a day.

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Fungal Keratitis After Radial Keratotomy

Steven L. Maskin, M.D., and Eduardo Alfonso, M.D.

Bascom Palmer Eye Institute, Department of Ophthalmology, University of Miami School of Medicine.

Inquiries to Eduardo Alfonso, M.D., Bascom Palmer Eye Institute, P.O. Box 016880, Miami, FL 33101.

A 35-year-old woman had a history of Crohn's disease that was treated with sulfasalazine. The patient had six-incisional radial keratotomy of both eyes; the right eye in October 1990, and the left eye in January 1991. Postoperatively the right eye had done well. However, two weeks postoperatively, the left eye became red and irritated while on a regimen of antibiotic and corticosteroid drops. The surgeon noted an infiltrate in the central aspect of the 5 o'clock incision. The patient was treated with topical fortified cefazolin, fortified tobramycin, and dexamethasone without improvement. Cultures yielded no growth. On March 6, 1991, the patient was referred to a corneal specialist because of continued irritation and pain. A diagnosis of crystalline keratopathy was made. The wound at the 5 o'clock incision was irrigated with vancomycin (50 mg/ml). Vancomycin (50 mg) and gentamicin (40 mg) were injected subconjunctivally, and the patient was given topical fortified cefazolin, fortified tobramycin, Neosporin, and fluorometholone 0.25%. Repeat cultures yielded no growth. On March 18, 1991, she was referred to Bascom Palmer Eye Institute for examination and treatment of persistent keratitis. Visual acuity was 20/30 in the left eye. There was moderate bulbar conjunctival injection with ciliary flush. The 5 o'clock incision had a mid to deep stromal feathery white infiltrate with overlying epithelial defect (Figure). There were small keratic precipitates on the underlying endothelium. The anterior chamber was not inflamed. Tension was 16 mm Hg by pneumotonometry. The posterior segment was normal. The patient was admitted to the hospital after undergoing corneal scraping for smears and culture. Topical ciprofloxacin

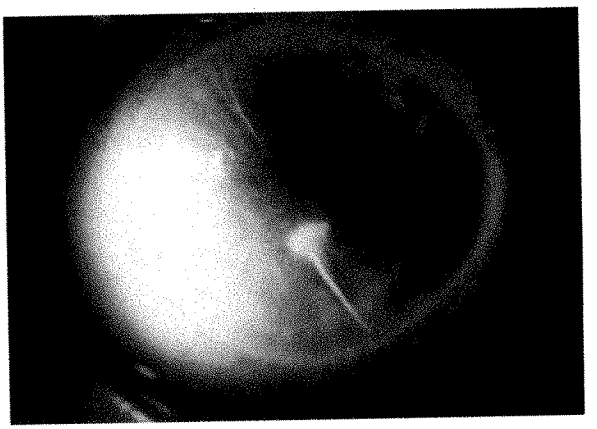


Figure (Maskin and Alfonso). Stromal infiltrate with overlying epithelial defect at the 5 o'clock incision, three months after radial keratotomy.

every 30 minutes was started. Cultures were positive for *Candida parapsilosis*. The patient was then treated with topical amphotericin B (0.5%), one drop every 30 minutes, and ketoconazole, 200 mg orally three times a day. The patient had daily epithelial scrapings while in the hospital to provide optimal penetration of the amphotericin B to the deep corneal stroma. By the fourth day of therapy, there was marked improvement in symptoms, as well as a decrease of the infiltrate. On follow-up examination, approximately one month later, she was symptom-free, with a best-corrected visual acuity of 20/20. The infiltrate was less dense with an intact epithelium. Amphotericin B, 0.5%, was tapered to every four hours and she continued the ketoconazole, 200 mg orally three times a day.

Infectious keratitis is one of the most visually significant complications to occur after radial keratotomy surgery. Maintenance of good vision (greater than 20/40) relies on early identification and institution of appropriate therapy.[1,2] Bacterial keratitis may occur early, within the first few postoperative weeks, or late.[1,2] Early-onset cases are mainly caused by gram-positive cocci (60%), whereas the majority of late-onset cases (62%) are caused by gramnegative rods.[2] The early onset of fungal keratitis after radial keratotomy in our patient suggests the inoculum occurred during the intraoperative or early postoperative period. The routine use of postoperative topical corticosteroids may dispose the wounded cornea to growth of fungal organisms. Our patient had no

known agricultural or other direct exposure to fungal elements. Infectious keratitis after radial keratotomy may be caused by nonbacterial microbes as in all cases of microbial keratitis, and it warrants comprehensive cultures.

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Fig. 1 (Brunette and Stulting). *Sporothrix schenckii* scleritis. An area of scleral necrosis was present near the nasal corneoscleral limbus at the 9 o'clock meridian.

Sporothrix schenckii Scleritis

Isabelle Brunette, M.D., and R. Doyle Stulting, M.D.

Emory Eye Center, Emory University School of Medicine. Supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York, New York.

Inquiries to R. Doyle Stulting, M.D., Emory Eye Center, 1327 Clifton Rd. N.E., Atlanta, GA 30322.

A 40-year-old healthy white man was struck in the left eye by a flying chip of wood on Dec. 21, 1987. Two months later, his eye became progressively red and painful and a diagnosis of episcleritis was made on Feb. 2, 1988. After failure to respond to treatment with topical dexamethasone, he was referred to us for further examination.

When first seen at the Emory Eye Center on April 4, 1988, the patient's visual acuity was R.E.: 20/15 and L.E.: 20/20. The left eye showed moderate conjunctival injection and chemosis. An area of scleral necrosis was present near the nasal corneoscleral limbus at the 9 o'clock meridian (Fig. 1). No foreign body was found. Gram stain of a scraping from the necrotic sclera disclosed thick-walled yeast forms (Fig. 2). Treatment was begun with miconazole, 10 mg/ml every hour topically, and 15 mg subconjunctivally. By April 18, inflammation had progressed and the eye had become more painful. Miconazole was replaced by amphotericin B topically (2.5 mg/ml every hour), intravenously (0.25 mg/kg of body weight/day increased to maximal daily doses of 0.6 mg/kg of body weight), and subconjunctivally (0.75 mg every other day for three doses). On April 21, the Centers for Disease Control identified the organism as *Sporothrix schenckii*. Administration of a saturated solution of potassium iodide was started at ten drops orally three times a day, increasing by two drops every other day up to a daily dose of 24 drops three times a day. By April 29, the scleral ulcer bed was clean, firm, vascularized, and 40% of normal thickness. On June 1, all medications were discontinued. Since then, the eye has been uninflamed and visual acuity is 20/20.

Sporothrix schenckii is a dimorphic fungus. Diagnosis is made by cultures on Sabouraud's agar where cream to black, folded colonies develop within three to five days. The fungus lives as a saprophyte on vegetation. Typically, after an incubation period of three to 40 weeks, a red papule appears on the hand or other exposed body surface. It progresses to a pustule and ulcerates. The infection may remain localized or more frequently, spreads along the lymphatics, resulting in a series of subcutaneous nontender nodules that may ulcerate. This lymphocutaneous form is far more frequent than the pulmonary form (resulting from inhalation of airborne spores) and the hematogenously disseminated form of sporotrichosis. Sporotrichosis is a potentially lethal infection.

Ocular infections are most frequently limited to eyelids and conjunctiva, although severe infection may gain access to any part of the eye, either by exogenous or endogenous routes.

In 1928, De Caralt[1] described a yellowish

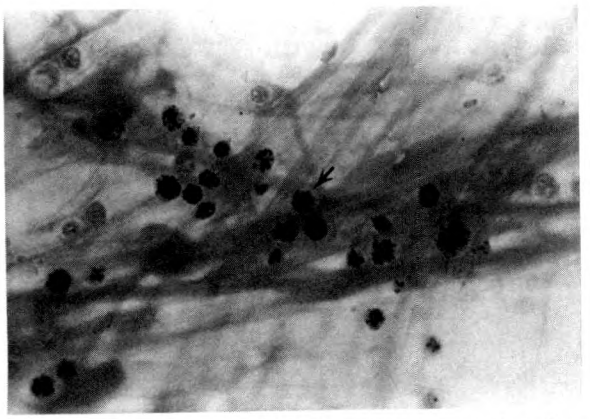


Fig. 2 (Brunette and Stulting). Gram stain of a scraping from the necrotic sclera disclosed thick-walled yeast forms (arrow) (× 400).

paralimbal scleral nodule with secondary corneal infiltration that was thought to be sporotrichotic because of the nodular manifestation and the efficacy of potassium iodide therapy, but the diagnosis was never proven by culture. Secondary infiltration[2] or perforation[3] of the sclera has been described in association with intraocular sporotrichosis, but sclera is generally resistant to sporotrichotic invasion. Often it is one of the last preserved structures in eyes otherwise extensively destroyed by necrotizing endophthalmitis caused by *S. schenckii*.[4,5]

Iodide therapy remains the treatment of choice in cutaneous and lymphocutaneous sporotrichosis, as in infections of the eyelids and conjunctiva. A typical dose is 15 drops three times a day of a saturated solution of potassium iodide (usually 50 mg per drop), with gradual increases to 30 or 40 drops three times a day. Iodide therapy should be continued for at least one month after clinical recovery. Indigestion and iododermatitis are possible side effects. Amphotericin B appears to be superior to iodide therapy in extracutaneous and visceral infections and would be recommended in more severe intraocular and orbital infections, as well as in any ocular infection resistant to iodide therapy. All forms of the disease are poorly responsive to miconazole, flucytosine, and ketoconazole.

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Nocardial Scleritis

James G. Brooks, Jr., M.D., Richard A. D. Mills, F.R.A.C.O., and Douglas J. Coster, F.R.A.C.O.

Department of Ophthalmology, Flinders Medical Centre.

Inquiries to D. J. Coster, Department of Ophthalmology, Flinders Medical Centre, Bedford Park, South Australia 5042.

A 90-year-old woman underwent left extracapsular cataract extraction with anterior chamber intraocular lens implantation on Dec. 11, 1990. Chloramphenicol 0.5% and prednisolone phosphate 0.5% drops were instilled postoperatively. One week later, however, necrotic scleritis of the temporal perilimbal region was noted. Initial intensive therapy with topical and oral cephalexin was unsuccessful and the area was surgically debrided. Microbiologic studies disclosed no organisms. Because of continued inflammation, repeat scrapings were performed but again failed to isolate an organism. Oral administration of corticosteroids resulted in a marked improvement in scleral inflammation, but attempts to taper the dosage resulted in recurrence of inflammation.

On referral to our institution on Jan. 16, 1991, the patient's medications included 75 mg of prednisone per day and topical dexamethasone, twice a day. Best-corrected visual acuity was 20/80 in the left eye, and slit-lamp examination showed a large area of temporal scleral thinning with ischemic and necrotic borders (Fig. 1). Examination of scrapings demonstrated

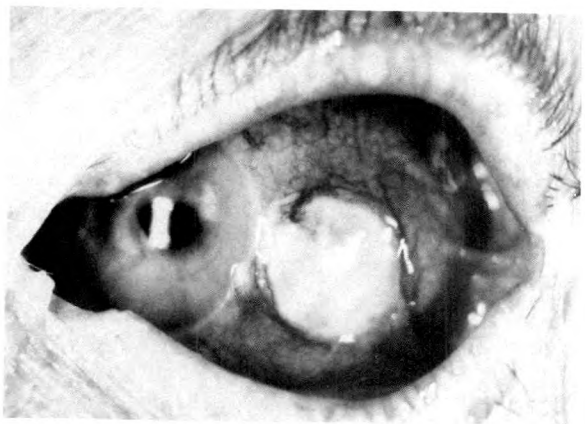


Fig. 1 (Brooks, Mills, and Coster). Slit-lamp photograph of necrotic scleral abscess at initial examination.



Fig. 2 (Brooks, Mills, and Coster). Resolution after surgical debridement with scleral grafting and prolonged medical therapy.

gram-positive filamentous bacteria with some branching. Results of serologic tests were negative for autoimmune disease. Treatment with hourly topical (100,000 U/ml) and intravenous penicillin G (3 million units every four hours) was begun with tapering of treatment with oral corticosteroid. *Nocardia asteroides* was isolated 48 hours later and treatment was changed to topical administration of an intravenous preparation of a trimethoprim/sulfamethoxazole combination product and amikacin (10 mg/ml) with an oral double-strength trimethoprim/sulfamethoxazole combination product, twice a day.

Improvement on tapering of treatment was noted until six weeks later, when the patient demonstrated worsening inflammation. New foci of scleral necrosis were found adjacent to the previously involved area, and repeat cultures were positive for nocardiae. Surgical debridement with donor scleral grafting was performed. Postoperative treatment with topical and oral antibiotics was continued, with resolution of the scleral necrosis and inflammation over a period of several weeks. Six months postoperatively, in the absence of antibiotic therapy, there is no evidence of recurrence (Fig. 2).

Nocardia, an aerobic gram-positive and weakly acid-fast filamentous bacterium, is a soil saprophyte often found in decaying organic matter.[1] The organism grows slowly in culture on a variety of nonantibiotic-enriched media. *Nocardia* is an uncommon human pathogen, with infection usually manifesting in immunocompromised individuals as nocardiosis.[2] Dissemination to the skin, central nervous system, and abdominal viscera can occur. Ocular infections caused by nocardiae include conjunctivitis, keratitis, endogenous or exogenous endophthalmitis, and scleral buckle-associated scleritis.[3,4] Our patient had postoperative scleritis presumably caused by scleral inoculation with nocardiae at the time of cataract extraction. Nocardiae are sensitive to sulfonamides, penicillin, tetracycline, and amikacin, with the sulfonamides generally regarded as first-line therapy. This case demonstrates an unusual but serious complication of cataract extraction. It also emphasizes the need for identification of the causative organism, as well as the need for prolonged medical therapy in combination with surgical debridement in cases of infectious scleritis.[5]

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Preseptal Cellulitis Caused by *Nocardia brasiliensis*

Lee R. Hunter, M.D., Andrew H. Krinsky, M.D., and Carola H. Fleener, M.D.

Sarasota, Florida.

Inquiries to Lee A. Hunter, M.D., Eye Specialists, 1428 S. Tamiami Trail, Sarasota, FL 34239.

Nocardia species represent an uncommon group of pathogens responsible for a wide variety of skin and systemic infections.[1-3] We treated a patient who had clinical signs of preseptal cellulitis at initial examination and who eventually developed culture-proven *Nocardia* abscesses.

The patient was an 11-year-old boy first seen by his local physician one week after manipulation of a skin pustule below the lateral right lower eyelid by his mother. Records indicated that at initial examination moderate edema and erythema were present in the right upper and lower eyelids and some surrounding skin. There was also a slight amount of purulent eyelid margin discharge. At that time, preseptal cellulitis was diagnosed. Blood culture, conjunctival swab culture, and a complete blood cell count were performed. Treatment with an intramuscular injection of ceftriaxone along with oral cefaclor was begun. The patient continued oral medication for two days and returned to one of us (C.H.F.) for follow-up. A history of worsening periocular edema, pain, and erythema of the right preseptal area was obtained, and an indurated area of the inferolateral right lower eyelid was noted on physical examination. The patient was referred that day for ophthalmic consultation to one of us (L.R.H.).

His visual acuity was 20/20 in each eye. The globe was normal. There was a 10 × 5 × 3-mm fluctuant subcutaneous abscess of the inferolateral right lower eyelid. Edema and erythema extended from this area to involve the entire ocular adnexa, creating the appearance of preseptal cellulitis. Approximately 3 cm posterior to the lateral orbital rim, another subcutaneous fluctuant area could be palpated. This lesion was 10 mm in diameter, and was elevated 4 mm. It was surrounded by less intense skin inflammation. There was a raised, enlarged, and tender preauricular lymph node. Moderate submandibular lymphadenopathy was noted. Orbital computed tomography showed strictly subcutaneous involvement and reflected the marked edema of the preseptal area and the two subcutaneous abscesses. The patient was taken to the operating room and given general anesthesia. Careful inspection of the two abscesses disclosed small skin drainage sites, which would allow expression of only small amounts of purulent material with massage. Small incisions through these sites with a blade into the fluctuant abscess disclosed a moderate amount of purulent material that was sent for culture and sensitivity testing. A sterile drain was left at each site. For the next two days, the patient was treated with intravenous nafcillin and cefotaxime. Although the abscesses did not redevelop, there was little clinical improvement. Initial results of the conjunctival culture disclosed *Enterobacter aerogenes* and *E. cloacae*. Infectious disease consultation was obtained (A.H.K.), and treatment with nafcillin was changed to oral trimethoprim and oral sulfamethoxazole. By the next day, the preseptal edema had improved moderately. The next day, the initial culture of the surgical specimen disclosed *Nocardia* organisms. Treatment with cefotaxime was then discontinued and amikacin was administered intravenously. The infection eventually was confirmed to be caused by *N. brasiliensis*. For the next three days the clinical signs decreased to normal and the drains were pulled. Treatment with amikacin was discontinued and the patient was discharged to continue oral trimethoprim and sulfamethoxazole therapy. At no point in the clinical course was the patient febrile.

Several features of this case are consistent with the nocardial skin infections described in the literature. The cause is often a contaminated skin wound. In our patient the presence of two *Enterobacter* species in the conjunctival culture indicated the poor hygiene with which his eye was treated. The infection is usually slow, progressive, and often creates multiple subcutaneous abscesses in a line. This has been referred to as sporotrichoid nocardiosis.[4] Lymph node involvement is usually marked. Drainage through the skin from the abscess may be present. The clinical features that distinguished our case from the usual manifestation of preseptal cellulitis were the subcutaneous abscesses, which were not found before the day of admission, and marked lymphadenopathy of both the preauricular and submandibular area. This case did share features with preseptal cellulitis secondary to skin wound in general.

Nocardia organisms should be considered in patients who have preseptal cellulitis with fea-

tures of isolated areas of subcutaneous induration and lymphadenopathy at initial examination. Recognition is important, because the choice of antibiotics for nocardial infection differs markedly from the choice of antibiotics for the usual organisms creating preseptal cellulitis.

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Brucellosis and Uveitis

Jonathan Walker, M.D., Om P. Sharma, M.D., and Narsing A. Rao, M.D.

University of Southern California School of Medicine and Doheny Eye Institute.

Inquiries to Narsing A. Rao, M.D., Doheny Eye Institute, 1355 San Pablo St., Los Angeles, CA 90033.

Brucellosis is a bacterial infection transmittable from animals to humans, mainly through exposure to infected carcasses, abortus, and unpasteurized dairy products. With the advent of modern animal health measures and pasteurization, the incidence has declined dramatically, although cases are still described (131 cases in 1984).[1] Brucellosis was once considered an important cause of uveitis, and is still diagnosed occasionally in more rural countries.[2] However, as the incidence of brucellosis has declined, so has the diagnosis of the related uveitis, and recent discussions usually refer to the previous literature for descriptions.[3-5] Given the scarcity of cases and the uncertainty of the previous diagnostic techniques, some authorities have questioned whether brucellosis truly causes uveitis.[3,4] We recently managed a case of brucellosis that did lead to uveitis, and we suggest that *Brucella* organisms be considered a potential, albeit uncommon, cause of uveitis.

A 56-year-old man had a ten-week history of recurrent fevers, night sweats, and right upper quadrant pain at referral to our institution. He had a history of travel to many rural areas, but he denied any known exposure to sick animals or suspect foods. At initial examination, he had already undergone an extensive examination at several medical facilities that culminated in a liver biopsy that showed necrotizing granulomas. He had been treated empirically with ampicillin, metronidazole, isoniazid, and rifampin for various presumed causes of disease without effect. The diagnosis of brucellosis was entertained and titers for *Brucella* organisms were positive at 1:640. Treatment was begun with tetracycline and within two weeks, he had recovered and was back at work. Follow-up titers were 1:80. After three weeks of treatment, he noted floaters and cloudy vision. He was treated with topical corticosteroids for bilateral iritis, and he was referred to the uveitis service at Doheny Eye Institute. On examination, his visual acuity was R.E.: 20/50 and L.E.: 20/40. Scattered pigmented keratic precipitates and posterior synechiae were present in both eyes. The anterior chambers were uninflamed (he was using topical corticosteroids) but he had moderate anterior vitreous cells; there was mild disk hyperemia and scattered yellow, round choroidal lesions in the periphery of each eye (Figure). Because he had already had a full systemic examination, no additional testing was deemed necessary. He was treated with a six-month tapered dose of oral and topical corticosteroids, to which he had a good response. He had one brief recurrence of uveitis two years later that responded quickly to topical treatment. He ultimately developed posterior subcapsular cataracts and underwent uncomplicated extracapsular cataract extraction and posterior chamber lens implantations; he has had no further episodes of uveitis and has remained in good health.

Patients with brucellosis usually have systemic symptoms of malaise, fevers, chills, night sweats, headaches, and arthralgias at initial examination. The acute phase, if not treated, can become chronic or relapsing.[1] The diagnosis is based largely on the clinical signs and symptoms and on positive titers; skin tests are



Figure (Walker, Sharma, and Rao). Well-circumscribed lesions in periphery of the choroid.

not helpful and the organism may be difficult to culture.[1] Brucellosis uveitis generally develops after the acute phase and consists variably of a chronic iridocyclitis, nummular keratitis, multifocal choroiditis, and optic neuritis.[5] With the exception of uncommon metastatic endophthalmitis, the ocular manifestations are considered a noninfectious immune response. Our case supports this hypothesis, and was one in which the uveitis began after a clinical cure had been achieved with antibiotics. We believe that this case represents a true brucellosis-related uveitis on the basis of the clinical signs and symptoms, temporal association with treatment, lack of recurrence, and lack of other identifiable causes.

Treatment of brucellosis uveitis consists simply of nonspecific anti-inflammatory agents, such as topical corticosteroids, once the systemic disease has been controlled with antibiotics (usually tetracycline and streptomycin).[5] Persons at risk for this disease include abattoir workers, veterinarians, and those who eat unpasteurized dairy products. Travelers to developing countries and to rural areas are also at risk, and a particular susceptibility has been noted in travelers who are being treated for an ulcer.[1] We believe brucellosis can cause a uveitis, and that this knowledge mandates exploring the work, food, and travel history as part of the general approach to a patient with uveitis.

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In Situ Detection of Human Herpesvirus 6 in Retinitis Associated With Acquired Immunodeficiency Syndrome

Isabelle Reux, M.D., Anne-Marie Fillet, M.D., Henri Agut, M.D., Christine Katlama, M.D., Jean-Jacques Hauw, M.D., and Phuc LeHoang, M.D.

Raymond Escourolle Neuropathology Laboratory (I.R., J.-J.H.), Virology Laboratory (A.-M.F., H.A.), Department of Infectious Diseases (C.K.), and Department of Ophthalmology (P.LeH.), Groupe Hospitalier La Pitié-Salpêtrière. Supported by grants from the National Institute of Health (Dr. LeHoang); Institut Nationale de la Sauté et de la Recherche Médicale U360, Paris, France (Dr. Hauw); the Agence Nationale de Recherche sur le SIDA, Paris, France (Drs. Hauw and Agut); the Association Claude Bernard, Paris, France (Drs. Hauw and Agut); and the Fédération Française des Aveugles, Paris, France (Dr. Reux). Presented in part at the meeting of the Société Française de Neuropathologie, Paris, France, Dec. 9, 1991.

Inquiries to Isabelle Reux, M.D., Laboratoire de Neuropathologie Raymond Escourolle, Groupe Hospitalier La Pitié-Salpêtrière, 83 boulevard de l'Hôpital, 75013 Paris, France.

Human herpesvirus 6 was first isolated in 1986 from the peripheral blood leukocytes of

patients with acquired immunodeficiency syndrome (AIDS) and lymphoproliferative disorders in the United States.[1] Recently, human herpesvirus 6 infection was associated with interstitial pneumonitis after bone marrow transplantation,[2] which suggested a causative role of this virus in some opportunistic infections. The human herpesvirus 6 genome has been detected by polymerase chain reaction in the DNA extracted from retinal tissue of patients with AIDS.[3] By immunohistochemical methods, we detected human herpesvirus 6 in the retinas of two patients with AIDS who had cytomegalovirus-induced retinitis at initial examination.

Case 1

A 30-year-old homosexual man who was seropositive for human immunodeficiency virus (HIV) developed cytomegalovirus retinitis in the left eye on Jan. 26, 1990, and was treated with foscarnet (12 g/day for two months, then 6 g/day for three months). Cytomegalovirus retinitis appeared in the right eye and the foscarnet dosage was increased to 12 g/day until Aug. 28, 1990, when the dosage was decreased again to 6 g/day. Because of a penis ulceration on Jan. 3, 1991, treatment with foscarnet was replaced by ganciclovir (300 mg/day), which was stopped on Jan. 13, 1991, because of an aplasia. Ganciclovir (400 μg) was then injected intravitreally in the left eye, twice a week. Five days before death, ophthalmic examination showed active retinitis in the left eye and cicatricial retinitis in the right eye. The patient died from septic shock on March 22, 1991.

Case 2

A 34-year-old homosexual man who was seropositive for HIV had bilateral inferior cytomegalovirus retinitis at initial examination on Nov. 29, 1989, and was treated with foscarnet (12 g/day). He died on Dec. 29, 1989, from bilateral bronchopneumonia.

Both eyes of both patients were removed at autopsy. The left eye of the patient in Case 1 and the right eye of the patient in Case 2 were frozen in isopentane cooled by liquid nitrogen and kept at −80 C. The eyes were cut into two parts with an electrical metal saw. Contiguous 10-μm cryostat sections were obtained and fixed in formaldehyde for hematoxylin and eosin staining or in acetone for immunohistochemical analysis. For localization of human herpesvirus 6 and cytomegalovirus antigens, sections were incubated with mouse monoclonal antibodies OHV1 (K. Yamanishi, M.D., Research Institute for Microbial Diseases, Osaka

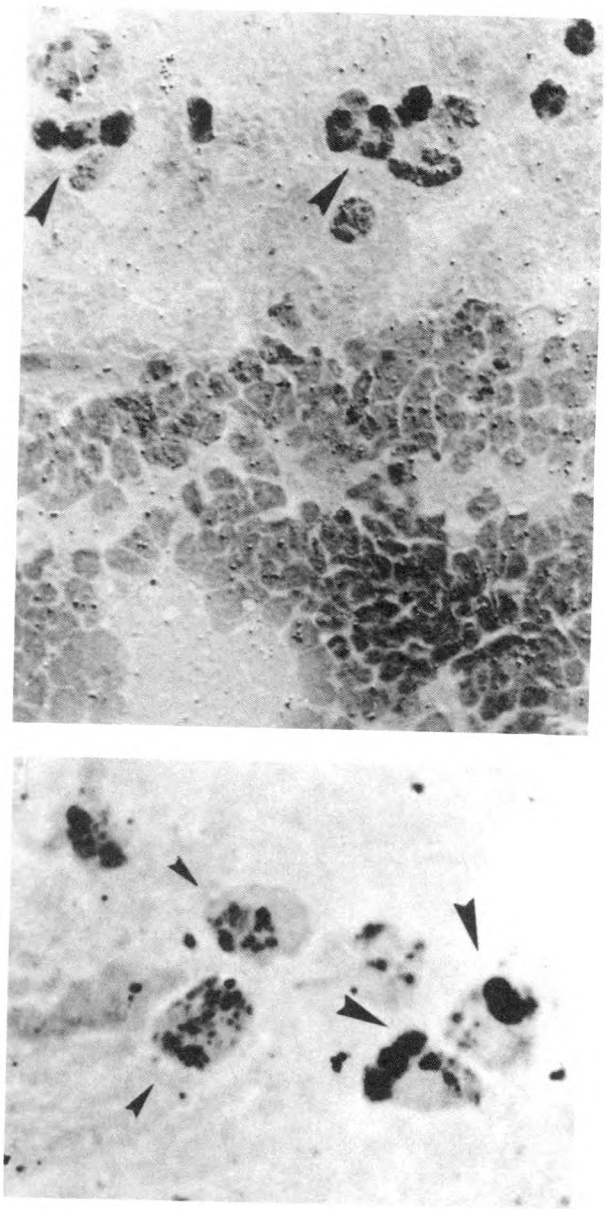


Figure (Reux and associates). Immunohistologic detection of human herpesvirus 6-infected cells in neurosensorial retina from a patient with AIDS and retinitis. Top, Human herpesvirus 6 antigens in ganglion cell layer (Nomarski's interference optics, × 800); arrowheads indicate clusters of human herpesvirus 6-infected cells. Bottom, Detail of nuclear human herpesvirus 6 staining; large and small arrowheads indicate large and small nuclear inclusions, respectively (× 2,000).

University, Osaka, Japan) and E13 (Biosoft, Paris, France), then stained with a three-step indirect immunoperoxidase method. Control procedures included the study of eye sections from an HIV-seronegative patient without retinitis, the use of respiratory syncytial virus antibody as an irrelevant monoclonal antibody, and immunoperoxidase staining in the absence of primary antibody. Positive control specimens included human herpesvirus 6-infected lymphocytes, cytomegalovirus-infected human fibroblastic cells, and cytomegalovirus-infected brain tissue.

Histologic examination of both eyes showed typical cytomegalic cells within the zones of retinal necrosis, and in the adjacent tissue. Cells positive for human herpesvirus 6 antigen were in the retina of the two patients and were mainly located in the ganglion cell layer (Figure, top). Some human herpesvirus 6-positive cells were also observed in the inner nuclear cell layer. Various human herpesvirus 6-specific staining aspects included cytoplasmic and nuclear small granulations or large inclusions (Figure, bottom); they could have been caused either by different stages of viral infection or by the different section levels. Cytomegalovirus antigens were detected on adjacent sections in the two cases.

Our immunohistologic detection of human herpesvirus 6 in the retinas of patients with AIDS was unique; it was parallel to detection of cytomegalovirus. A crossreactivity of monoclonal human herpesvirus 6 antibody has been excluded by a previous study[4] and other data (I.R., unpublished data, 1991). The human herpesvirus 6 and cytomegalovirus retinal coinfection in patients with AIDS and retinitis is thus authenticated. Human herpesvirus 6 could be an opportunistic agent leading to retinitis during AIDS. The in vitro sensitivity of human herpesvirus 6 to available antiviral agents[5] requires that the potential opportunistic role, especially in the retina, be explored. Currently, a study is being undertaken to correlate clinical data and results obtained by immunohistochemical analysis, in situ hybridization, and polymerase chain reaction.

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Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Prophylactic Use of Apraclonidine for Intraocular Pressure Increase After Nd:YAG Capsulotomies

EDITOR:

In the article, "Prophylactic use of apraclonidine for intraocular pressure increase after Nd:YAG capsulotomies," by D. E. Silverstone, S. F. Brint, K. W. Olander, R. B. Taylor, G. R. McCarty, J. M. deFaller, and L. L. Burk (Am. J. Ophthalmol. 113:401, April 1992), the authors showed apraclonidine to be effective in attenuating the incidence of severity of increases in intraocular pressure in the first three hours after the treatment. However, I have several clinical cases to illustrate the need to use caution in concluding the lack of a deleterious pressure increase if one considers only the immediate postoperative hours. I treated three patients with apraclonidine before a YAG

capsulotomy. Subsequent pressure checks at two to three hours were unremarkable. However, each of these three patients had a marked increase on a pressure determination at 24 hours.

These patients all had previous uncomplicated extracapsular extractions with posterior chamber lens implantation. The preoperative pressures were 10, 20, and 22 mm Hg, respectively. The last patient, suspected of having glaucoma, had a normal optic nerve and visual field. One drop of apraclonidine was given to each patient 20 to 30 minutes before the procedure was performed. One drop of prednisolone acetate was given postoperatively and continued three times a day for one week. Pressures were checked two to three hours after the laser procedure and again at 24 hours. To achieve a central capsulotomy in each of these three patients, 34, 13, and 17 mJ were used, respectively. The pressures at three hours were 13, 20, and 21 mm Hg, respectively.

On the first postoperative day these patients had a marked visual improvement with comfortable eyes, an anterior chamber reaction of trace to mild cells, and pressures of 43, 50, and 49 mm Hg, respectively. Gonioscopy performed on the first two patients disclosed widely open aphakic angles. The pressures responded in each patient to topical beta-blockers and carbonic anhydrase inhibitors. Pressures were controlled within several hours to levels between 20 and 22 mm Hg. All patients have subsequently done well and did not require medications after the first week.

The course of these patients indicates that one may get a false sense of reassurance that an intraocular pressure spike has not occurred after a YAG capsulotomy if one only checks the pressure several hours after treatment. If one is concerned about the deleterious effects of a pressure increase, then it would appear that a determination at 24 hours would be helpful in identifying those few patient in whom the protective effect of apraclonidine in transitory.

ANDREW ROMANOWSKI, M.D.
Portland, Oregon

Reply

EDITOR:

We appreciate Dr. Romanowski's response to our article. Dr. Romanowski relates his experience with three patients in whom there was significant increase in intraocular pressure one day, but not three hours after Nd:YAG laser capsulotomy. We concur with Dr. Romanowski's point that there may be patients who demonstrate no significant pressure increase within the first several hours after laser treatment who may have increases one day later.

Several factors were considered in the design of our study. There were reports that the maximal mean postlaser increase in intraocular pressure occurred during the first several hours after the procedure.[1-3] In a study conducted by one of us,[3] incidence of pressure increases ($\geq$ 10 mm Hg) within the first several hours after capsulotomy was 38% (eight of 21 patients). At 24 hours it was 0% (none of 20 patients).[3] In a report of 32 patients, all of the eyes with an increased pressure at 24 hours above baseline also had an increase within the first several hours.[2] In another study of 37 capsulotomies, none of the patients with a pressure increase less than 5 mm Hg during the first four hours after capsulotomy had an increase above 10 mm Hg at a later time.[1] The maximal ocular hypotensive effect of apraclonidine occurs within two to five hours after installation, with effects lasting at least 12 hours.[4,5] Thus, the time-course of the treatment and of the condition seemed to be a good match.

Concerning the medication regimen used by Dr. Romanowski, one drop of apraclonidine was instilled 20 to 30 minutes before laser treatment. In our study, we instilled two drops of apraclonidine, which is consistent with the currently approved product labeling: one drop one hour before the procedure and one drop immediately afterward. It is interesting to note reports that apraclonidine, when used in conjunction with cataract extraction, is not effective unless dosed one hour preoperatively.[7,8] Dr. Romanowski also used prednisolone acetate, three times a day, for one week after laser treatment, whereas we did not. An increased pressure within one day after start of corticosteroid therapy is early for a classic corticosteroid-responder glaucoma. Nevertheless, it is difficult to assess its role in these cases.

We reported that prophylactic use of apraclonidine decreased the incidence of increases in intraocular pressure after laser treatment. We did not, however, intend readers to infer that such treatment provides an abolition of these increases at all times in all patients. The significance of Dr. Romanowski's deviation from label protocol is also not assessed here. In addition to the cases provided by Dr. Roman-

owski, Nesher and Kolker[6,7] described a patient, treated prophylactically with apraclonidine, who had no significant increased pressure one hour after procedure, but had a significant increase one day later. We concur with previous suggestions that patients with severe glaucomatous damage be seen not only immediately after laser treatment, but also 24 hours later.[8] Dr. Romanowski's comments allow us to expand on the interpretation of our report.

DAVID E. SILVERSTONE, M.D.
New Haven, Connecticut
STEPHEN F. BRINT, M.D.
New Orleans, Louisiana
KENNETH W. OLANDER, M.D.
Milwaukee, Wisconsin
ROBERT B. TAYLOR
GEORGE R. McCARTY, Ph.D.
JOSEPH M. deFALLER
Fort Worth, Texas
LINDA L. BURK, M.D.
Dallas, Texas

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Argon Laser Treatment of Trichiasis

EDITOR:

The article, "Argon laser treatment of trichiasis," by G. B. Bartley and J. C. Lowry (Am. J. Ophthalmol. 113:71, January 1992), reported a recurrence rate of 41% in a retrospective study of 44 patients treated by argon laser. Laser variables included 1.10-W power, 50- to 100-μm spot size, 0.2-second duration, and blue-green wavelength. The depth of vaporization was not mentioned.

In a recent prospective study of 60 patients,[1] a recurrence rate of 11.6% was reported. Laser variables were 1.5-W power, 100-μm spot size, and 0.5-second duration. Vaporization was carried out to a depth of 2.0 to 2.5 mm in a plane just superior to the postorbicular fascia.

Recurrences were most often caused by inadequate depth of vaporization and less frequently by unpredictable follicle position (for example, posttraumatic lash malposition). We believe a depth gauge is helpful in assuring adequate laser treatment, and its routine use may improve treatment outcome and reproducibility. Finally, we have modified our technique and now use the laser in the continuous mode at a power of 2.5 W. This change permits more rapid lash ablation (six to ten pulses) and limits contiguous vaporization. A recurrence rate of 11.6% compares favorably to cryoablation.[2] We agree with the authors that laser ablation is best suited to isolated, aberrant cilia.

M. DOUGLAS GOSSMAN, M.D.
RUDY YUNG, M.D.
A. JAN BERLIN, M.D.
JOSEPH R. BRIGHTWELL, M.D.
JOHN W. WILLIAMS, M.D.
Louisville, Kentucky

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Reply

EDITOR:

The criterion we used for successful treatment was unequivocal ablation of treated cilia in an eyelid. Therapy was judged to have failed if any aberrant eyelashes subsequently appeared, even if a misdirected cilium may have represented new rather than recurrent trichiasis.

We agree with Dr. Gossman and associates that most recurrences result from inadequate depth or intensity of laser treatment. The depth of the laser burns in the patients we treated was approximately 2 to 3 mm but the power, spot size, and duration of each pulse were less than that used by Dr. Gossman and colleagues.[1] In another recent report in which more conservative laser parameters were used (0.3 W, 0.5-second duration, 50-μm spot size, and 40 to 50 burns per eyelash), secondary treatment was necessary in 29 of 77 patients (38%).[2]

Since we reviewed our results, we have used a larger spot size (100 μm) and an increased number of burns (up to 50 per follicle). An additional feature of the technique described by Dr. Gossman and associates that may promote eyelash ablation is to deliver several defocused, 200-μm burns to the base of the follicle. In appropriately selected patients, more intensive treatment appears to improve success without increasing the frequency of complications. Dr. Gossman and colleagues should be congratulated on their excellent therapeutic results.

GEORGE B. BARTLEY, M.D.
JONATHAN C. LOWRY, M.D.
Rochester, Minnesota

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Sculpting of Hydroxyapatite Implants—Correction

EDITOR:

In the article, "Sculpting of hydroxyapatite implants" (Am. J. Ophthalmol. 113:453, 1992), I mentioned in the text that the caliper used for sculpting was a Green caliper. I have since learned that the correct name is a Jameson caliper. I regret this mistake, and thought I should bring it to the attention of readers of THE JOURNAL.

MONT J. CARTWRIGHT, M.D.
Ann Arbor, Michigan

BOOK REVIEWS

Edited by Mark J. Mannis, M.D.

Atlas of Orbital Surgery. By Charles R. Leone, Jr., Arthur S. Grove, Jr., William C. Lloyd III, and Ted H. Wojno. Philadelphia, W. B. Saunders, 1992. 187 pages, index, illustrated. $70

Reviewed by JACK ROOTMAN
Vancouver, British Columbia

This text by well-known ophthalmic plastic and orbital surgeons sets as two of its major goals the production of a concise and accurate guide with a step-by-step approach to commonly performed orbital procedures, and a review of major aspects of the examination and diagnosis of orbital disease.

The book is divided into five sections, the first of which is a review of surgical anatomy and clinical investigation. The second focuses on the major approaches to the orbit; the third focuses on surgery for Graves' orbitopathy; and the fourth section focuses primarily on surgery for trauma and fractures. The fifth section deals with the management of specific orbital disorders.

In terms of the authors' wish to produce a step-by-step and integrated illustration of orbital procedures, the book is well constructed. The individual in need of studying the common orbital procedures will be able to find guidance from the illustrations and descriptions given in the book. This will, however, assume some foreknowledge of the character of the tissues of the eyelids and orbit and of the basic management of these tissues. Little guidance is given regarding details of the various disease processes that may be encountered, making the text somewhat less useful for the true novice.

As to the discussion of surgical anatomy, I thought there was not a strong enough attempt to develop a clear visualization that would allow the novice an anatomical context for the surgical procedures described. The discussion of the general principles of orbital surgery and choices of approach is brief and may fail to provide the intellectual framework for surgical decision making.

Regarding recommended surgical methodology, there are a number of areas in which there may be some controversy. Additionally, although the illustrations and the text are well-linked, there are some inaccuracies in visual perspective as drawn. For example, the illustration of the neurosurgical approach depicts excessive traction on the frontal lobe. In the case of the medial approach to orbital decompression, the position of the anterior ethmoid artery is not only too high, but appears anterior to the usual location. The authors would do well to describe in the text the usual key landmarks that allude to the specific surgery. In the various descriptions of surgical procedures for specific diseases, the authors present their approaches well, particularly in relationship to trauma.

There is some lack of emphasis on alternative approaches to management of certain disorders, such as mucoceles, hemangiomas, cystic lesions, capillary hemangiomas, combined interventional neuroradiologic techniques in the management of arteriovenous lesions, and the collapsing of large and complex bony tumors. The lumping of so-called orbital pseudotumor with lymphoproliferative masses, and a failure to be more specific about the range of disorders that fall under this confusing rubric, may be difficult for the novice. The question of indications for various types of orbital exenteration is only briefly dealt with and could be enhanced.

Although it falls short in terms of breadth of approach and clarity of illustration, this book does stick to its principles of providing an atlas approach to orbital surgery and should be available to seasoned surgeons as well as residency training programs.

Clinical Decisions in Neuro-Ophthalmology, ed. 2. By Ronald M. Burde, Peter J. Savino, and Jonathan D. Trobe. St. Louis, Mosby Year Book, 1992. 466 pages, index, illustrated. $89

Reviewed by STEVEN A. NEWMAN
Charlottesville, Virginia

Taken literally, neuro-ophthalmology is the study of the afferent and efferent connections responsible for processing visual information obtained from the eye and simultaneously controlling the direction of ocular alignment. In another and important sense, however, neuro-ophthalmology can be viewed simply as a method of approaching clinical problems. In this text, now in its second edition, the authors

choose not to address neuro-ophthalmology on the basis of long lists of differential diagnoses and pathophysiology, but rather to instruct in methods of approaching clinical problems. As such, the authors' goal is to teach the reader how to think.

This edition has been enlarged by almost 25% with six new chapters. This increase has been accomplished largely by expanding into chapters subjects that were previously dealt with in smaller sections. Thus, visual loss now is expanded into four separate chapters including unexplained visual loss, prechiasmal visual loss, chiasmal visual loss, and postchiasmal visual loss. Similarly, previous sections on comitant and incomitant strabismus are now separate chapters. One completely new chapter deals with visual illusions and hallucinations. This may be the best chapter in the book. It has superb illustrations including some extremely creative photography. Chapters on proptosis, headache, and pupillary abnormalities have been updated.

New to this edition are "management boxes," which graphically highlight methods of case management. This encapsulation technique has the drawback of suggesting too strongly the one best way of handling a problem. To be fair, reasons for the authors' decisions, as well as alternative approaches, are then given more fully in the text. Nonetheless, in any book of this nature, attempts at simplification will lead to selective focus. The decision trees have been improved. Changes in the type face make them easier to read. Technology, an anathema to some classical neuro-ophthalmologists, has gained a greater presence in this edition. The uses of automated static perimetry, potential acuity testing devices, and imaging studies have been introduced or have received greater attention. Management flow diagrams, including that for managing idiopathic pseudotumor cerebri, acknowledge the interventional aspects of neuro-ophthalmology.

Several appendices are also new. These include directions on performing some of the fundamental clinical testing procedures. Items not discussed in detail in the first edition have regained their proper status and include, for example, a more detailed discussion of traumatic optic neuropathy and Duane's syndrome. The quality of the index has been improved, providing an additional road map through the material for those with insufficient time to read it in its entirety.

Many of the ten color plates are completely unchanged. Others have only minor modifications. In some instances much better examples were found. Syndromes that did not exist at the time of the last edition, such as multiple evanescent white dot syndrome, are included.

Although the cookbook approach to any problem has its own set of potential shortcomings, and we might quibble with some of the details to the flow diagrams, this text remains one of the most useful and lucid approaches to neuro-ophthalmic disease. It should be required reading for those students who want to know what neuro-ophthalmology is. Others might benefit as well from this reasoned approach to clinical decision-making.

Fluorescein Angiography. Technique, Interpretation, and Application. By Max Nanjiani. New York, Oxford University Press, 1992. 130 pages, index, illustrated. $68

Reviewed by STEVEN COHEN
Miami, Florida

"Fluorescein angiography is now as important to an ophthalmologist as the chest x-ray is to the physician," states the author. This book endeavors to make angiographic interpretation as simple and straightforward as the reading of a chest x-ray. The author intends this text for residents and general ophthalmologists as a guide to interpretation of fluorescein angiograms. Fluorescein angiographic technique and application are covered in an organized, well thought out, and concise manner. Each chapter is clearly written. The multitude of attractive and classic photographs will appeal to most ophthalmologists, who revel in good photography.

The book begins with a brief historical overview and the basic principles of angiography. The author discusses several aspects of fluorescein angiography not often addressed by other texts. For example, thoughtful discussion is given to the indications and contraindications of angiography. The second chapter deals with the requirements of a fluorescein angiography unit, including necessary equipment and support personnel. This section is important to any ophthalmologist planning to perform fluoresce-

in angiography. An excellent flow chart on the management of collapse during or after fluorescein angiography is presented. The third and fourth chapters focus on interpretation of fluorescein angiograms and classification of abnormal fluorescence. These chapters are well illustrated with classic examples of both angiography and matching fundus photographs.

The next five chapters of the book cover broad categories of retinal disease. Diabetic retinopathy, macular disease, optic nerve disease, vascular disorders, and tumors are included. These chapters contain excellent examples of classic angiographic findings in patients with these conditions. The single weakness of these chapters is that, in an attempt to cover too much, the subjects are treated superficially. For example, in the nine-page chapter on diabetes, diagnosis and treatment of background retinopathy, preproliferative retinopathy, proliferative retinopathy, and three types of macular edema are discussed. These chapters would be most valuable to the beginning resident. Despite the somewhat superficial coverage of each topic, the discussion of the fluorescein angiographic findings in each disease provides an excellent overview. The book concludes with an interesting and thorough description of iris angiography, a topic not covered in detail by most texts.

This book is an excellent introduction to fluorescein angiography for anyone unfamiliar with the technique. It also serves as an outstanding review for ophthalmologists who want an update on current wisdom concerning performance, application, and interpretation of this important diagnostic technique.

The Eye In General Practice, ed. 9. By C. R. S. Jackson and R. D. Finlay. New York, Churchill Livingstone, 1991. 178 pages, index, illustrated. $39.95

Reviewed by JOSHUA GUTMAN
Attleboro, Massachusetts

According to Lynn Payer, in "Medicine and Culture," the most striking feature of the British health system is its economy. "The Eye in General Practice" demonstrates this economy as a major virtue in describing fundamentals of ophthalmology for the family physician. The authors' goal to provide "a textbook which sets out the commoner problems clearly and concisely" has been admirably accomplished. Since time devoted to ophthalmology is limited in medical school as well as in many family practice residencies, a guide to primary care of the eye may be a useful addition to the generalist's library. "The Eye in General Practice" has much to praise and little to criticize.

The first asset of this text is its organization. Its first two chapters on history, examination, and initial assessment give a fine overview of common conditions. Excellent tables of differential diagnosis constitute the substance of Chapter 2. The next seven chapters cover the eye anatomically from the eyelids to the retina. Nine chapters follow that deal with specific eye disorders, including glaucoma, oculomotor problems, and trauma, as well as other ophthalmic areas of interest to primary care, for example, spectacles and contact lenses, blindness, and special investigations.

The authors' approach is strictly practical. The how-to paragraphs are numerous and well done. For example, the instructions on performing a Schirmer's test are the clearest I have read. A lucid procedure for removing a contact lens is another useful aid for those of us who do not wear them. On the other hand, this volume has no academic pretensions. There are no citations, no references, and therefore no assistance for a reader who wishes to pursue greater knowledge on a particular topic. In the chapter on special investigations, descriptions of modern ophthalmologic diagnostic procedures can assist those of us many years out of training in communicating appropriate information to our patients who need referral.

The most significant advantage of this text over most ophthalmology chapters in primary care texts is in the illustrations. Jackson and Finlay have included numerous excellent photographs and diagrams. The book concludes with a somewhat idiosyncratic glossary of terms, but a superb index.

A disadvantage of this text relates to its origin in the United Kingdom. For a family physician trained in the United States, many of the medication recommendations, particularly for antibiotic usage, are not drugs of choice. Topical chloramphenicol, for example, is used in the United Kingdom, whereas we in the colonies prefer alternative drugs. Detailed instructions for the general practitioner on excising chalazia

seem misdirected for the training and experience patterns of family physicians in the United States. There is also a frustrated tone about the therapy of such a common entity of blepharitis: "Treatment is tedious." However, a recommendation from my ophthalmologist brother-in-law advising scrubbing of the eyelids with baby shampoo has frequently worked for my patients. A personal quibble with the style of the text is the notable absence of humor. It lacks the wit sprinkled throughout British medical literature.

Nonetheless, family physicians in training, as well as those of us in practice, can use this excellent text as a complete guide to the diagnosis of common, as well as some uncommon, eye problems. In certain instances, a domestic primary care text may be needed to supplement choices of therapy.

Books Received

Spanish-English, English-Spanish Medical Dictionary. By Onyria Herrera McElroy and Lola L. Grabb. Boston, Little, Brown and Company, 1992. 506 pages. $27.50

This attractive paperback book is more than just a Spanish-English, English-Spanish medical dictionary because it contains a lucid 25-page summary of Spanish grammar. It will be an extremely useful tool for the physician who attempts to communicate with Spanish-speaking patients in their own language. Although not oriented specifically to ophthalmology, the book contains all the essential terms for an effective ophthalmologic anamnesis.

ABSTRACT DEPARTMENT

Edited by George B. Bartley, M.D.

Uveal melanoma. Therapeutic consequences of doubling times and irradiation results. A review. Manschot, W. A.*, and van Strik, R.: Int. Ophthalmol. 16:91, 1992.

The authors expressed concern about the appropriateness of radiotherapy for melanoma based on their review of published studies of the calculated doubling times for uveal melanomas, the histologic characteristics of irradiated melanomas, and patient survival and preservation of vision after radiotherapy. Previous studies demonstrated that the doubling time is at least 60 days and that death by metastases occurs 35 to 40 doubling times after dissemination; the authors therefore reasoned that irradiation cannot influence survival data within the first seven posttreatment years because all metastatic deaths during this interval likely would be caused by pretreatment tumor metastasis. Additionally, microscopically viable melanoma tissue has been found in 215 of 231 eyes (93%) that previously had been irradiated. Because of these concerns and their assessment that preserved vision in irradiated eyes is "generally poor," the authors concluded that radiotherapy for posterior uveal melanoma is not justified at sites other than those associated with the Collaborative Ocular Melanoma Study, with the following exceptions: (1) small melanomas distant from the fovea and optic nerve, (2) patients with a life expectancy less than six years, (3) tumor in a single functioning eye, and (4) patients who refuse enucleation. Data from more than ten years of follow-up are needed to analyze appropriately the long-term survival of patients treated for uveal melanoma.—George B. Bartley

*Institute of Pathology, Erasmus University, P.O. Box 1738, 3000 DR, Rotterdam, The Netherlands.

Results of a randomized controlled trial of carotid endarterectomy for asymptomatic carotid stenosis. Mayo Asymptomatic Carotid Endarterectomy Study Group*: Mayo Clin. Proc. 67:513, 1992.

A randomized controlled trial was designed to compare the effects of carotid endarterectomy with medical treatment using low-dose acetylsalicylic acid (80 mg/day, orally) in patients with asymptomatic carotid stenosis (≥50% linear stenosis or 75% cross-sectional area stenosis in one or both internal carotid arteries). Among 71 randomized and 87 eligible nonrandomized patients, the total ipsilateral perioperative stroke and death rate was 0% among randomized patients and 3% among nonrandomized patients, and the major stroke and death rate was 0% for both groups. Too few cerebral ischemic events occurred to judge the comparative effectiveness of carotid endarterectomy vs low-dose acetylsalicylic acid. The trial was terminated early because of a significantly higher number of myocardial infarctions and transient cerebral ischemic events, which were secondary end points of the study, in the surgical group than in the medical group. Most of the events were not temporally related to the surgical procedure; but there was evidence that these events could have related to the absence of acetylsalicylic acid use in the surgical group. These observations reinforce the appropriateness of acetylsalicylic acid use during the perioperative period and beyond (unless contraindications exist) in patients with asymptomatic carotid stenosis who undergo carotid endarterectomy.—George B. Bartley

*D. O. Wiebers, M.D., Department of Neurology, Mayo Clinic, Rochester, MN 55905.

Light and retinopathy of prematurity. Does retinal location offer a clue? Fielder, A. R.*, Robinson, J., Shaw, D. E., Ng, Y. K., and Moseley, M. J.: Pediatrics 89:648, 1992.

Nursery illumination has been implicated in the pathogenesis of retinopathy of prematurity (ROP), although the results of recent studies are conflicting. The data base for this article is a prospective ROP study on 607 infants of birth weight ≤1700 g including 35 larger siblings from multiple births when 1 infant fulfilled the birth weight criteria. Retinopathy commences preferentially in the nasal retina of the most immature neonate and is less likely to develop, or its onset is delayed, in the superior and inferior regions. These findings cannot be fully

accounted for by regional vascular and neuroanatomical variations. Radiometric and physiological evidence suggests that the very immature neonate, most at risk of developing severe ROP, receives the greatest retinal irradiance. Furthermore, ROP commences in the areas of the retina receiving the highest light dose, and its onset is either retarded or inhibited in the darker retinal regions. Further studies are required to determine whether early exposure to light is a factor in the development of ROP. If a causal relationship is proven, here at least is one modality that can easily and immediately be controlled.—Authors' abstract

*Birmingham and Midland Eye Hospital, Church St., Birmingham B3 2NS, England.

Postural disturbances due to homonymous hemianopic visual ataxia. Rondot, P.*, Odier, F., and Valade, D.: Brain 115:179, 1992.

Patients with homonymous hemianopsia often complain of disturbances of equilibrium. To investigate the role of vision in postural control, the authors measured body sway on a force moment measuring platform in patients with either right or left homonymous visual field defects, normal patients whose right or left visual fields were occluded, patients with anterior brain lesions without visual field defects, and normal control patients. Hemianopsia increases lateral oscillations in the standing position and alters posture to shift the body's center of gravity toward the hemianopsia. The authors referred to this postural instability as "visual ataxia" and hypothesized that vision, especially peripheral vision, has a tonic influence on posture in each visual hemifield. Visual ataxia does not appear to be of labyrinthine origin and is not related to the presence or absence of foveal vision. There is a limited potential for improvement in abnormal posture and equilibrium over time.—George B. Bartley

*Service de Neurologie, Centre Hospitalier Sainte Anne, 1 rue Cabanis, 75674 Paris, Cedex 14, France.

Temporoparietal fascial flap for orbital and eyelid reconstruction. Ellis, D. S., Toth, B. A.*, and Stewart, W. B.: Plast. Reconstr. Surg. 89:606, 1992.

Temporoparietal fascial flaps have been used in auricular reconstruction and as free tissue transfers for distant reconstruction. The flap is supplied by the anterior branch of the superficial temporal artery and can be harvested readily through either a coronal incision or a scalp incision. The authors described six patients in whom a temporoparietal fascial flap was used successfully for orbital or lower eyelid reconstruction. Compared with the temporalis muscle or the temporalis fascia, a temporoparietal fascial flap is advantageous in that it is vascularized by an axial blood vessel, can be fashioned thinner and longer, is more mobile, and does not cause a donor site depression in the temporalis fossa. Potential complications include localized alopecia because of dissection near hair follicles, decreased venous drainage, or injury to the facial nerve.—George B. Bartley

*2100 Webster St., Suite 424, San Francisco, CA 94115.

Cortical blindness in children. Utility of flash VEPs. McCulloch, D. L., and Taylor, M. J.*: Pediatr. Neurol. 8:156, 1992.

In two previous articles in Pediatric Neurology there was disagreement regarding the value of flash visual-evoked potentials in predicting the visual prognosis in children with acute cortical blindness. The authors reviewed the studies and concluded that the discrepancy resulted from differences in the inclusion criteria for the patients who were examined. Flash visual-evoked potentials have predictive value only in patients with sudden-onset cortical blindness that is not attributable to previous trauma, infection, or hypoxia. The test results are frequently abnormal in patients with underlying neurologic disease even when visual acuity is good, which weakens the test's prognostic usefulness. In the patients studied, normal flash visual-evoked potentials were always associated with partial or full visual recovery, absent visual-evoked potentials portended a poor prognosis, and visual outcomes with abnormal visual-evoked potentials were variable.—George B. Bartley

*Division of Neurology, Hospital for Sick Children, 555 University Ave., Toronto, Ontario, Canada M56 1X8.

Precision radiation therapy for optic nerve sheath meningiomas. Eng, T. Y.*, Albright, N. W., Kuwahara, G., Akazawa, C. N., Dea, D., Chu, G. L., Hoyt, W. F., Wara, W. M., and Larson, D. A.: Int. J. Radiat. Oncol. Biol. Phys. 22:1093, 1992.

The treatment of optic nerve sheath meningioma is controversial and is usually individualized for each patient. Although meningiomas are typically considered to be relatively radioresistant, radiation therapy has been useful in some instances. Radiotherapy for optic nerve lesions usually involves two laterally opposed fields or wedged pairs. The authors developed a new technique that allows radiation to be administered more precisely, and they advocate the method for the treatment of unilateral optic nerve lesions. The patient is supine. The patient's head is rotated and immobilized with a custom-made mask and support system so that the affected optic nerve is approximately perpendicular to the horizontal plane. The treatment table rotates about the vertical axis, which allows treatment of a smaller tissue volume while reducing incident radiation to the pituitary gland, optic chiasm, and contralateral optic nerve, lens, and cornea. Three patients with optic nerve meningioma and one patient with a juvenile pilocystic astrocytoma were treated with this method; the radiation dose was 5,400 cGy at 180 cGy per day, five days per week. The primary disadvantage of the technique is the effort required to make the immobilization mask.—George B. Bartley

*Department of Radiation Oncology, University of California, School of Medicine, San Francisco, CA 94143-0412.

Measurement of globe position in complex orbital fractures. I. A modification of Hertel's exophthalmometer, using the external auditory canal as a reference point. Yeatts, R. P.*, van Rens, E., and Taylor, C. L.: Ophthalmic Plast. Reconstr. Surg. 8:114, 1992.

Measurement of globe position in complex orbital fractures. II. Patient evaluation utilizing a modified exophthalmometer. Yeatts, R. P.: Ophthalmic Plast. Reconstr. Surg. 8:119, 1992.

The measurement of the position of the globe within the orbit usually may be assessed accurately by Hertel or Naugle exophthalmometers, which use the lateral orbital rims or the superior and inferior orbital rims, respectively, as stable points of reference. Quantitating globe position in complex orbital trauma is difficult, however, because of disruption of the facial skeleton. The authors modified a Hertel exophthalmometer to use the external auditory canals as stable reference points. Enophthalmos was documented in more than 80% of patients with bilateral comminuted orbital and facial fractures (pyramidal and craniofacial dysjunction fractures), suggesting the need for early surgical repair. Conversely, because enophthalmos was relatively uncommon in patients with tripod fractures, the authors recommended selective, rather than routine, orbital floor exploration with these fractures.—George B. Bartley

*Wake Forest University Eye Center, Medical Center Blvd., Winston-Salem, NC 27157-1033.

Hepatitis B and hepatitis C in emergency department patients. Kelen, G. D.*, Green, G. B., Purcell, R. H., Chan, D. W., Qaqish, B. F., Sivertson, K. T., and Quinn, T. C.: N. Engl. J. Med. 326:1399, 1992.

To determine the prevalence of infection with hepatitis B virus, hepatitis C virus, and the human immunodeficiency virus type 1 in an unselected but well-defined population, the authors tested the sera of 2,523 adult patients who were admitted to an inner-city emergency department during a six-week period. Six hundred twelve patients (24%) were infected with at least one of the three viruses. Seropositivity for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus type 1 was 5%, 18%, and 6%, respectively. At least one viral marker was found in approximately 30% of the patients who were actively bleeding or in whom procedures were performed. Routine screening for human immunodeficiency virus type 1 would have failed to identify 87% of the patients infected with hepatitis B virus and 80% of those infected with hepatitis C virus. Percutaneous exposure to these viruses poses an occupational risk to health care providers, and the rate of acquisition of hepatitis B virus among unvaccinated individuals may be approximately 50% to 100% greater than the rate for human immunodeficiency virus type 1. Strict adherence to universal precautions and vaccination against hepatitis B virus were recommended.—George B. Bartley

*Department of Emergency Medicine, Marburg B186, Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21205.

Case records of the Massachusetts General Hospital (Case 21-1992). N. Engl. J. Med. 326:1417, 1992.

A 65-year-old man had a three-year history of gradually worsening visual acuity in the right eye and an 18-month history of recurrent, painless diplopia that resolved spontaneously. His medical history was contributory only for adequately treated hypertension. Magnetic resonance imaging disclosed a large, homogeneous, gadolinium-enhancing mass of the sphenoid sinus, clivus, right infratemporal fossa, upper nasopharynx, right cavernous sinus, and right middle cranial fossa. A biopsy specimen was consistent with plasmacytoma of bone; additional laboratory and clinical examinations confirmed the diagnosis of multiple myeloma. Radiotherapy was administered to the skull base lesion, followed by chemotherapy with melphalan and prednisone. The differential diagnosis included primary tumors of the sphenoid sinus, mucocele, esthesioneuroblastoma, nasopharyngeal carcinoma, lymphoma of the skull base, granulocytic sarcoma, angiofibroma, chordoma, chondrosarcoma, chondroma, osteogenic sarcoma, fibrous dysplasia, epidermoid tumors, cholesterol cyst, cholesteatoma, a metastatic tumor, a pituitary neoplasm, craniopharyngioma, rhabdomyosarcoma, meningioma, tumors of nerve origin, intracranial vascular anomalies, paraganglioma, chemodectoma, hemangioma, hemangiopericytoma, and inflammatory lesions.—George B. Bartley

Blind spots. Ramachandran, V. S.*: Sci. Am. 266(5):86, 1992.

According to legend, King Charles II of England amused himself by visually decapitating his ladies-in-waiting by appropriately positioning his normal blind spot. The author of this paper reviewed the results of several experiments involving blind spots that were designed to test how the brain interpolates visual information. For example, when a small disk on a colored background is positioned such that the disk falls within an eye's blind spot, the disk is perceived as being covered by the color of the surrounding field. This phenomenon, which is termed "filling in," is one manifestation of a more general perceptual mechanism known as surface interpolation. The brain's perception of patterns involving the blind spot is altered, however, by induced illusions of contour or motion. Filling in occurs early in visual processing and it involves the generation of a perceptual representation (in contrast to a conceptual representation). The similarities and differences between normal blind spots and scotomas that result from cerebral cortex disease are currently under investigation.—George B. Bartley

*Department of Psychology and Neurosciences, University of California at San Diego, San Diego, CA 92103.

Medical therapy for ocular allergy. Trocme, S. D.*, Raizman, M. B., and Bartley, G. B.: Mayo Clin. Proc. 67:557, 1992.

The ocular manifestations of allergy have traditionally been classified into four categories—namely, hay fever conjunctivitis, vernal keratoconjunctivitis, atopic keratoconjunctivitis, and contact lens-associated giant papillary conjunctivitis. Typically, hay fever conjunctivitis is characterized by mild conjunctival inflammation, whereas the other disorders may have severe inflammation and clinical manifestations. Potentially blinding corneal complications may result from vernal keratoconjunctivitis and atopic keratoconjunctivitis. Although hay fever conjunctivitis is clearly an immediate hypersensitivity reaction, the immunologic mechanisms that cause vernal keratoconjunctivitis, atopic keratoconjunctivitis, and giant papillary conjunctivitis are primarily unknown and speculative. Treatment of patients with ocular allergies is often challenging and may necessitate collaborative efforts of an ophthalmologist and an allergist. Herein we discuss conventional therapy and new, promising antiallergy drugs.—Authors' abstract

*University of Texas Medical Branch, Room 340, Clinical Sciences Bldg. G-87, Galveston, TX 77550.

Terson's syndrome. A reversible cause of blindness following subarachnoid hemorrhage. Garfinkle, A. M.*, Danys, I. R., Nicolle, D. A., Colohan, A. R. T., and Brem, S.: J. Neurosurg. 76:766, 1992.

Terson's syndrome, the association of vitreous hemorrhage with subarachnoid hemor-

rhage, has been postulated to result from compressive obstruction of the central retinal vein and retinochoroidal anastomoses by an effusion of cerebrospinal fluid in the retrobulbar optic nerve sheath. Of 22 consecutive patients with subarachnoid hemorrhage, six patients (27%) had intraocular hemorrhage. Subarachnoid bleeding originated from aneurysmal rupture of the anterior communicating artery in three patients, from the anterior choroidal artery in one patient, from the middle cerebral artery in one patient, and from head injury in one patient. Vitreous blood was present in four of the six patients (six of eight eyes) at initial examination, whereas in the remaining two patients (three of four eyes) subhyaloid hemorrhages progressed to vitreous hemorrhage within 12 days. In one patient, intraocular bleeding was discovered before the clinical features of subarachnoid hemorrhage evolved. Two of the six patients died from complications of subarachnoid hemorrhage, but the presence of vitreous hemorrhage was not a statistically significant risk factor for increased mortality, in contrast to previous studies. Of the four survivors, visual acuity improved gradually over six months in three patients and one patient responded well to vitrectomy.—George B. Bartley

*Department of Ophthalmology, Sir Mortimer B. Davis Jewish General Hospital, 3755 Cote Ste. Catherine, Montreal, Quebec H3T 1E2, Canada.

Biological roles of nitric oxide. Snyder, S. H.*, and Bredt, D. S.: Sci. Am. 266(5):68, 1992.

The key role of nitric oxide in a variety of physiologic mechanisms has been studied intensively during the past five years. Not to be confused with nitrous oxide, nitric oxide is a short-lived (six to ten seconds) molecule that is formed from arginine and is converted by oxygen and water into nitrates and nitrites. The chemical has been identified in macrophages, where its free-radical toxicity can combat tumors and bacteria; in blood vessel endothelium, where it apparently acts as the principal regulator of blood pressure by causing vasodilation via the formation of the second messenger cyclic guanosine monophosphate; in the myenteric plexus, which controls peristalsis; and in approximately 2% of the neurons in the cerebral cortex. Unlike most neurotransmitters, which usually are stable chemicals that are stored in synaptic vesicles, nitric oxide has a unique mode of action and may represent a new class of neuronal messenger. Nitric oxide probably is synthesized on demand, crosses the synapse and enters the postsynaptic neuron by simple diffusion, and binds to iron within the enzyme, guanylate cyclase. The molecule may have a role in learning and memory. Additionally, inhibitors of nitric oxide synthetase may be of therapeutic benefit in the prevention of neurologic damage associated with excess glutamate release in stroke.—George B. Bartley

*Department of Neurosciences, Johns Hopkins University School of Medicine, Baltimore, MD 21205.

Interferon alfa-2a therapy for life-threatening hemangiomas of infancy. Ezekowitz, R. A. B.*, Mulliken, J. B., and Folkman, J.: N. Engl. J. Med. 326:1456, 1992.

Although interferon alfa-2a was developed as an antiviral agent, investigators noticed during clinical trials with the drug in patients with the acquired immunodeficiency syndrome that Kaposi's sarcoma was unexpectedly improved. The authors treated 17 patients with life-threatening hemangiomas and three patients with vision-threatening hemangiomas with daily subcutaneous injections of interferon alfa-2a (up to 3 million units/m^2 of body-surface area). All patients had failed to respond to a two-week course of corticosteroid therapy (2 mg/kg of body weight/day). The hemangiomas regressed by 50% or more after approximately eight months of interferon treatment in 18 of the 20 patients. In the three patients with periorbital hemangiomas, all of whom had exophthalmos, the amounts of regression were graded as 20%, 50%, and 60%, respectively. Side effects of therapy were transient and included fever (all 20 patients), neutropenia (one patient), and skin necrosis (one patient). The authors concluded that interferon alfa-2a appears to induce the early regression of corticosteroid-resistant hemangiomas of infancy.—George B. Bartley

*Department of Pediatrics, Children's Hospital, Enders Bldg., 7th Fl., 300 Longwood Ave., Boston, MA 02115.

In vivo gene transfer with retroviral vector-producer cells for treatment of experimental brain tumors. Culver, K. W.*, Ram, Z., Wallbridge, S., Ishii, H., Oldfield, E. H., and Blaese, R. M.: Science 256:1550, 1992.

One type of gene transfer therapy for the local treatment of cancer is to introduce into a proliferating tumor a gene that encodes a susceptibility factor that makes the lesion more sensitive to chemotherapy. With stereotaxic guidance, the authors injected herpes simplex thymidine kinase retroviral vector-producing murine fibroblasts into experimental cerebral gliomas in rats. The herpes genes were incorporated into the genomes of nearby dividing tumor cells and after five days the antiviral agent, ganciclovir, was administered intraperitoneally. Complete macroscopic and microscopic tumor regression was observed in 11 of 14 rats that had been treated with retroviral vector-producing cells, whereas ganciclovir had no effect on tumor growth in control rats. Normal nondividing brain tissues adjacent to the gliomas were not detectably harmed. This technique may have clinical application in the treatment of selected inoperable tumors.—George B. Bartley

*Cellular Immunology Section, Metabolism Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.

Vaccine protection of chimpanzees against challenge with HIV-1-infected peripheral blood mononuclear cells. Fultz, P. N.*, Nara, P., Barre-Sinoussi, F., Chaput, A., Greenberg, M. L., Muchmore, E., Kieny, M.-P., and Girard, M.: Science 256:1687, 1992.

Any potential vaccine against human immunodeficiency virus (HIV) must protect against infection by both cell-associated virus (infected cells) and cell-free virus. Previous studies demonstrated that chimpanzees could be immunized against infection with low doses of cell-free HIV. In the current report, the authors showed that chimpanzees could be protected against an intravenous challenge with peripheral blood mononuclear cells from a chimpanzee infected with HIV. One chimpanzee was immunized with whole inactivated HIV and two chimpanzees were vaccinated with purified antigens or antigens expressed by recombinant vaccinia viruses. No evidence of infection was detected after inoculation with cell-associated virus; antibody-dependent cellular cytotoxicity and antibody complement–mediated cytotoxicity were speculated to be the likely mechanisms of protection. One chimpanzee that had been virus-free for one year became infected, despite an apparently stable humoral response, after a second challenge with cell-free HIV-1. The authors noted that the frequent immunization regimen used in their study would be impractical for humans.—George B. Bartley

*Department of Microbiology, University of Alabama at Birmingham, Birmingham, AL 35294.

Risk factors for cyclosporine-induced nephropathy in patients with autoimmune diseases. Feutren, G.*, and Mihatsch, M. J., for the International Kidney Biopsy Registry of Cyclosporine in Autoimmune Diseases: N. Engl. J. Med. 326:1654, 1992.

To determine the incidence of and risk factors for nephropathy in patients treated with cyclosporine for autoimmune or inflammatory diseases, the authors studied data from renal biopsies performed in 192 patients (129 adults and 63 children) with insulin-dependent diabetes mellitus of recent onset, uveitis, psoriasis, Sjögren's syndrome, or polychronditis. The mean (± standard deviation) initial dosage of cyclosporine was 8.2 ± 2.8 mg/kg of body weight/day, and the median duration of treatment was 13 months (range, four to 39 months). Cyclosporine-induced nephropathy, defined as at least moderate focal interstitial fibrosis with tubular atrophy, arteriolar alterations, or both, was found in 21% of patients (37 adults and four children). The following three variables were demonstrated by multivariate logistic-regression analysis to be significant risk factors for the development of nephropathy: a high initial dose of cyclosporine, a large maximal increase in the serum creatinine concentration above baseline values, and increased age. The duration of increased serum creatinine concentration and the occurrence of increased blood pressure were not risk factors. The risk of nephropathy in patients with autoimmune disorders who are treated with cyclosporine may be reduced by avoiding dosages higher than 5 mg/kg of body weight/day and by preventing increases in serum creatinine greater than 30% above the patient's baseline value.—George B. Bartley

*Clinical Research/Immunology, Sandoz Pharma Ltd., 4002 Basel, Switzerland.

Phantom limbs. Melzack, R.*: Sci. Am. 266(4):120, 1992.

The perception of an arm or leg after the limb has been amputated is a common but poorly understood sensation. A related phenomenon, phantom vision, was first reported in 1769 by the philosopher Charles Bonnet, who described the visual experiences of his grandfather who had advanced cataracts. Phantom vision reportedly occurs in 15% of persons who lose all or part of their vision. The visual perceptions, which commonly include people and large buildings, appear when the eyes are open and usually are readily differentiated from residual, coexistent, true vision. The author reviewed various explanations that have been proposed to explain phantom limbs, phantom vision, and phantom hearing, and hypothesized that the phenomena result from as yet unproved interactions between the somatosensory receiving areas and the adjacent parietal cortex, the limbic system, and widespread cortical networks that are involved in cognitive activities such as self-perception and memory. The perception of phantom limbs, particularly by children who have been born without an arm or leg or who lose a limb at an early age, challenges the following two fundamental assumptions in psychology: that sensations are produced only by stimuli and that the perception of one's body results from sensory inputs that leave a memory in the brain. The author favors the presence in each individual of a unique, genetically determined "neuromatrix" or "neurosignature" that is modified by experience.—George B. Bartley

*Department of Psychology, McGill University, Montreal, Quebec, Canada H3A 2T5.

Preschool vision screening in pediatric practice. A study from the Pediatric Research in Office Settings (PROS) Network. Wasserman, R. C.*, Croft, C. A., and Brotherton, S. E.: Pediatrics 89:834, 1992.

In this cross-sectional study, the vision-screening process is described for 8417 children aged 3 to 5 seen for health supervision in a group of 102 pediatric practices in 23 states and Puerto Rico. Three hundred forty children who failed screening (63% of those who failed) were followed up 2 months after initial screening. The sample was 52% male, 86% white, 9% black, 3% Hispanic, and 1% Asian. Vision screening was attempted on 66% of children overall. Pediatricians' reasons for not screening were "not routine" (44%), "too young" (40%), and "screening done previously" (17%). Younger children were less likely to be screened than older children (39% of those aged 3), and Hispanics were less likely to be screened than other ethnic groups ($P < .001$). Thirty-three percent of children received no screening for latent strabismus. Two months later, 50% of parents whose child had failed a vision test were unaware of this fact on questionnaire follow-up. Eighty-five percent of children referred to an eye specialist had made or kept an appointment. It is concluded that pediatricians need to increase vision screening among younger preschool children and communicate more effectively to parents the results of screening failure.—Authors' abstract

*PROS Network, American Academy of Pediatrics, P.O. Box 927, 141 Northwest Point Blvd., Elk Grove Village, IL 60009-0927.

Tonic pupil, areflexia, and segmental anhidrosis. Two additional cases of Ross syndrome and review of the literature. Weller, M., Wilhelm, H., Sommer, N., Dichgans, J., and Wiethölter, H.*: J. Neurol. 239:231, 1992.

The triad of unilateral or bilateral tonic pupil, hyporeflexia, and segmental anhidrosis has been described as the Ross syndrome. The authors examined two patients with characteristic clinical features and reviewed 18 previously published cases. The syndrome is differentiated from other disorders of widespread autonomic dysfunction, such as Shy-Drager syndrome or Riley-Day syndrome, that may include the triad of Ross. Recent findings of hypohidrosis in many patients with Adie's syndrome, however, suggest that Ross syndrome may not be a distinct clinical entity.—George B. Bartley

*Psychiatrische Universitätsklinik, Füchsleinstrasse 15, W-8700 Würzburg, Federal Republic of Germany.

Current practice of cataract extraction and anaesthesia. Hodgkins, P. R.*, Luff, A. J., Morrell, A. J., Botchway, L. T., Featherston, T. J., and Fielder, A. R.: Br. J. Ophthalmol. 76:323, 1992.

A questionnaire regarding cataract extraction and anesthesia practices was sent in 1991 to

456 ophthalmologists in England and Wales and the results were compared with those of a similar survey completed by 318 ophthalmologists in 1985. Of the 456 ophthalmologists, 380 (83%) completed the new questionnaire. The use of extracapsular cataract extraction increased from 31% (98 of 318 respondents) in 1985 to 70% (266 of 380 respondents) in 1991, whereas during the same time interval, the percentage of ophthalmologists who performed intracapsular cataract extraction declined from 50% (158 of 318) to 2% (seven of 380). Of the 266 ophthalmologists who used extracapsular cataract extraction, 201 preferred a manual technique and 65 used an automated technique. Manual endocapsular extraction was used by 72 of 380 ophthalmologists (19%), an automated endocapsular technique was preferred by 15 of the 380 (4%), and eight of 380 ophthalmologists (2%) used phacoemulsification routinely. Intraocular lenses were implanted by 376 of 380 (99%) ophthalmologists in 1991, compared with 92% (291 of 318) in 1985. Local anesthesia (most commonly a retrobulbar block) was used routinely by 76 of the 380 (20%); the primary and secondary reasons for choosing local anesthesia were medical contraindications and patient preference, respectively. In 1985, general anesthesia was preferred by 212 of 318 respondents (67%), whereas in 1991 it was used frequently (more than 75% of cases) by 141 of 380 ophthalmologists (37%) and exclusively by six of 380 ophthalmologists (less than 2%). Perioperative sedation, more frequently oral than intravenous, was administered by 171 of 380 ophthalmologists (45%) for local anesthesia.—George B. Bartley

*Southampton Eye Hospital, Wilton Ave., Southampton, England SO9 4XW.

NEWS ITEMS

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The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

European Society of Ophthalmology: Xth Congress

The Xth Congress of the European Society of Ophthalmology will take place June 25–29, 1995, in Milano, Italy. For more information, write the Organizing Secretariat, Moretti, Rossi & Associati, Largo Settimio Severo, 4, 20144 Milano, Italy; fax 39-2-48021977.

Asia-Pacific Academy of Ophthalmology: XIV Congress

The XIV Congress of the Asia-Pacific Academy of Ophthalmology will take place Jan. 24–28, 1993, in Dhaka, Bangladesh. For more information, write the APAO Secretariat, OSB Bhaban, P.O. Box 8021, Mirpur, Dhaka-1216, Bangladesh; fax 880-2-804522.

Kaunas Medical Academy of Lithuania: VII Forum Ophthalmologicum Balticum—Ocular Trauma, Cataract Surgery, and Glaucoma

The Eye Clinic of Kaunas Medical Academy of Lithuania will hold its VII Forum Ophthalmologicum Balticum: Ocular Trauma, Cataract Surgery, and Glaucoma Oct. 29–31, 1992, in Kaunas, Lithuania. For further information, write Vyautas Jesinskas, M.D., VII Forum Ophthalmologicum Balticum, Kaunas Medical Academy Eye Clinic, Micheviciaus 9, Kaunas 233000, Republic of Lithuania.

American Diopter and Decibel Society: Biennial Meeting

The American Diopter and Decibel Society will hold its Biennial Meeting Jan. 16–23, 1993, at the Westin Camino Real in Puerto Vallarta, Mexico. For additional information, write Robin L. Wagner, American Diopter and Decibel Society, 3518 Fifth Ave., Pittsburgh, PA 15213; telephone (412) 647-2227; fax (412) 647-8720.

American Society of Ophthalmic Registered Nurses: Annual Meeting and Continuing Education Program

The American Society of Ophthalmic Registered Nurses will hold its Annual Meeting and Continuing Education Program Nov. 8–11, 1992, in Dallas, Texas. For further information, write ASORN, Inc., P.O. Box 193030, San Francisco, CA 94119; telephone (415) 561-8513.

Contact Lens Association of Ophthalmologists: Annual Meeting

The Contact Lens Association of Ophthalmologists will hold its Annual Meeting Jan. 13–16, 1993, at Ceasars Palace, Las Vegas, Nevada. For additional information, write Joyce Hanemann, CLAO, 523 Decatur St., New Orleans, LA 70130-1027; telephone (504) 581-4000; fax (504) 581-5884.

Dalhousie University: Parallel Pathways in the Visual System

The Department of Ophthalmology of Dalhousie University is sponsoring a symposium, Parallel Pathways in the Visual System, Oct. 2, 1992, in Nova Scotia, Canada. For more information, write Balwantray C. Chauhan, Ph.D., Nova Scotia Eye Centre, 1335 Queen St., Halifax, Nova Scotia, Canada H3J 2H6; telephone (902) 496-4343; fax (902) 496-2839.

Wilmer Ophthalmological Institute: Current Concepts in Ophthalmology

The Wilmer Ophthalmological Institute's Current Concepts in Ophthalmology will take place Dec. 10–12, 1992, in Baltimore, Maryland. For additional information, write the Program Coordinator, Johns Hopkins Medical Institutions, Office of Continuing Medical Education, Turner Bldg., 720 Rutland Ave., Baltimore, MD 21205; telephone (410) 955-2959.

Aspen Glaucoma Conference

The Aspen Glaucoma Conference will be held Sept. 30–Oct. 3, 1992 (new date), in Aspen, Colorado. For more information, write the Glaucoma Associates, 850 E. Harvard Ave.,

#205, Denver, CO 80210; telephone (303) 777-3653; or (800) 432-3653.

Cleveland Clinic Foundation: Current Concepts in Ophthalmology

The Cleveland Clinic Foundation will sponsor Current Concepts in Ophthalmology Dec. 4 and 5, 1992 (new date), in Cleveland, Ohio. For more information, write Donna Jackman, The Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH 44195-5242; telephone (216) 444-5696.

Hawaiian Eye Foundation: 14th Annual Royal Hawaiian Eye Meeting

The Hawaiian Eye Foundation will hold its 14th Annual Royal Hawaiian Eye Meeting Jan. 16–22, 1993, at the Westin Kauai, Lihue, Kauai. For further information, write the Hawaiian Eye Foundation, c/o Mary Charles & Associates, 2334 S. King St., Ste. 205, Honolulu, HI 96826; telephone (800) 942-9655.

Manhattan Eye, Ear & Throat Hospital: Glover-Lisman Professorship

The Department of Ophthalmology at the Manhattan Eye, Ear & Throat Hospital will hold the Glover-Lisman Professorship with guest lecturer Jack T. Holladay, M.D., Oct. 2 and 3, 1992, in New York City. For more information, write Kimberly Corbin, Dept. of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3760; fax (212) 753-7699.

New England Eye Center: Innovations in Clinical Ophthalmology

The New England Eye Center will offer a program, Innovations in Clinical Ophthalmology, Jan. 25–30, 1993, at the Grand Hyatt Wailea Resort and Spa, Maui, Hawaii. For more information, write Mark E. Keller, New England Eye Center, 750 Washington St., Box 450, Boston, MA 02111; telephone (617) 956-4621; fax (617) 956-4866.

New York University Medical Center: Alumni Day and Ocular Laser Surgery Symposium

The Department of Ophthalmology at the New York University Medical Center will hold its Alumni Day and Ocular Laser Surgery Symposium Oct. 10, 1992, in New York City. Stanley Chang will deliver the Harvey B. Taterka Lecture. For additional information, write Sheryl Arluk, New York University Post-Graduate Medical School, 550 First Ave., New York, NY 10016; telephone (212) 263-5294.

Alcon Research Institute Awards

The Alcon Research Institute is an entity dedicated to vision research. The institute is funded by Alcon Laboratories, Inc., but is directed by a fully independent Scientific Advisory Committee. An award of $100,000 was given to each of the following scientists in 1992: Joseph Caprioli, M.D., Yale University School of Medicine, New Haven, Connecticut; Deborah Carper, M.D., National Eye Institute, National Institutes of Health, Bethesda, Maryland; Robert W. Flower, Johns Hopkins University, Laurel, Maryland; Robert N. Frank, M.D., Kresge Eye Institute, Wayne State School of Medicine, Detroit, Michigan; Bernard Fung, Ph.D., Jules Stein Eye Institute, UCLA School of Medicine, Los Angeles, California; Alan M. Laties, M.D. (sharing award), University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; Jeremy Nathans, M.D., Ph.D., Johns Hopkins University, Howard Hughes Medical Institute, Baltimore, Maryland; Jerry Y. Niederkorn, Ph.D., University of Texas, Southwestern Medical Center, Dallas, Texas; Richard A. Stone, M.D. (sharing award), University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; Lubert Stryer, M.D., Stanford University School of Medicine, Stanford, California; and Robert N. Weinreb, M.D., Shirley Eye Center, University of California, San Diego, La Jolla, California.

Dana Center for Preventive Ophthalmology: Master's Degree Program

The Johns Hopkins Medical Institutions, under the auspices of the Dana Center for Preventive Ophthalmology (a World Health Organization Collaborating Center), will offer a special Master's Degree Program in Public Health specializing in Preventive Ophthalmology during the 1993–1994 academic year. The program is designed for individuals with ophthalmic experience or training interested in initiating, developing, and providing leadership to national or regional blindness-prevention activities and in conducting clinical epidemiologic research. For further information, write the Program Coordinator, Preventive Ophthalmology Program, DCPO, Wilmer Institute Room 116, Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21205; telephone (301) 955-2022.

Association for Research in Vision and Ophthalmology: Trustees Named

At the 1992 annual meeting of the Association for Research in Vision and Ophthalmology, Anita E. Hendrickson, Ph.D., of University of Washington, and Paul L. Kaufman, M.D., of the University of Wisconsin, were elected to the Board of Trustees. Dr. Hendrickson represents the Anatomy/Pathology Section and Dr. Kaufman represents the Glaucoma Section.

Texas Ophthalmological Association: 1992–1993 Officers

The Texas Ophthalmological Association elected the following officers for 1992–1993: David G. Shulman, president; Barry W. Uhr, president-elect; Sue Ellen Young, secretary; and Russell W. Neuhaus, treasurer.

Personals

Daniel M. Albert

Daniel M. Albert, David G. Cogan Professor of Ophthalmology at the Harvard University Medical School, has been named professor and chairman of the Department of Ophthalmology at the University of Wisconsin, effective July 1, 1992. Dr. Albert received a B.S. degree from the Franklin and Marshall College in 1958 and an M.D. degree from the University of Pennsylvania in 1962. He received an honorary M.A. degree from Harvard University in 1976. He was an intern and resident at the Hospital of the University of Pennsylvania, a United States Public Health Service Surgeon at the National Institutes of Health, and a special fellow in ophthalmic pathology at the Armed Forces Institute of Pathology. Dr. Albert was an assistant professor at Yale University School of Medicine and then transferred to Harvard Medical School. He is the author (with Harold Scheie) of the 9th edition of Textbook of Ophthalmology. In addition, he is the author of Jaeger's Atlas of Ophthalmology and Foundations of Ophthalmic Pathology.

David L. Epstein

David L. Epstein has been named chairman of the Department of Ophthalmology at Duke University Medical Center, Durham, North Carolina. Dr. Epstein received his M.D. from Johns Hopkins University in 1968. He was a resident at the Massachusetts Eye and Ear Infirmary and subsequently a fellow in glaucoma there. He was associate professor at Harvard University Medical School and most recently professor of ophthalmology at the University of California at San Francisco. Dr. Epstein is currently president of the Association for Research and Vision and Ophthalmology. He assumed his new position June 1, 1992.

Jay H. Krachmer

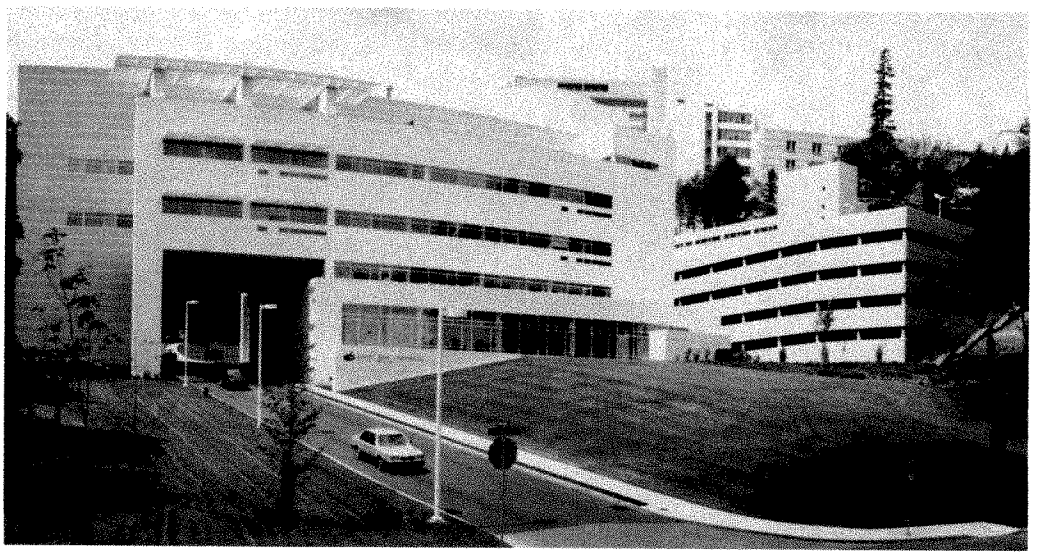
Jay H. Krachmer has been named professor and chairman of the Department of Ophthalmology at the University of Minnesota. He has also been named holder of the Mackall-Scheie Research Chair in Ophthalmology. The appointment became effective July 1, 1992. Dr. Krachmer previously was professor of ophthalmology at the University of Iowa. Dr. Krachmer is a graduate of Tulane University and was a resident in ophthalmology at the University of Iowa, following which he was a fellow at Wills Eye Hospital. He is a specialist in cornea and external diseases of the eye in addition to general ophthalmology.

Malcolm McCannel

Malcolm McCannel, clinical professor in the Department of Ophthalmology at the University of Minnesota, received the University's Alumni Service Award. Dr. McCannel received a master's degree in ophthalmology from the University of Minnesota in 1946. He also completed his residency training at the University. He has practiced ophthalmology in Minneapolis since 1949. From 1961 to 1972, he served on various missions for the World Health Organization's Project HOPE. Dr. McCannel is recognized nationally for his work in intraocular lens implantation and cataract surgery.

Lew Wasserman

The American Medical Association honored Lew Wasserman, chairman of Research to Prevent Blindness, with its Citation of a Layman for Distinguished Service at the annual meeting of the American Medical Association House of Delegates in Chicago on June 21, 1992. The award, which is the American Medical Association's highest honor for a nonphysician, was presented to Mr. Wasserman in recognition of his lifelong support of medical research and treatment through such institutions as Research to Prevent Blindness and the Jules Stein Eye Institute. Mr. Wasserman is chairman and chief executive officer of MCA Inc.



Casey Eye Institute

Casey Eye Institute: Dedication

The Casey Eye Institute on the campus of the Oregon Health Sciences University, Portland, Oregon, was dedicated Sept. 11, 1992. The 102,000-sq. ft. Casey Eye Institute is the seventh regional eye research institute sponsored by Research to Prevent Blindness. Its six levels include research laboratories, 60 examination and treatment rooms, six major and three minor operating rooms, together with state-of-the-art educational facilities. There is an adjacent 320-space parking structure for patients and staff.

The building was designed by the world-famous architect, Richard Meier. A dramatic two-story atrium extends through the outpatient waiting area. At its base is a contiguous glass floor of Caribbean-colored glass, designed and manufactured by James Carpenter, a New York glass artist. The facility, with its panoramic view of Mt. Hood and Mt. St. Helens, has already been featured in a Hollywood film.

The professional staff is headed by F. T. Fraunfelder, who has been chairman for the past 15 years. There are 18 M.D.s and ten Ph.D.s on the faculty. The facility includes the Robert Bedrossian, M.D., Cornea Clinic; the Leonard Christensen, M.D., Pathology Laboratory; and the Kenneth C. Swan, M.D., Educational Center, which includes a 150-seat auditorium, three conference rooms, and a library.

The $31 million in construction funds were provided primarily by grateful patients, national and local corporations, foundations, the Oregon State Elks Association, and a $1 million commitment from the faculty members of the Department of Ophthalmology. The National Institutes of Health provided a $1 million competitive construction grant, which was the only governmental, state, or federal funding.

Glove Perforations in Ophthalmic Surgery

Paul Prendiville, M.D., Peter J. McDonnell, M.D., and Paul P. Lee, M.D.

To determine the potential rate of intraoperative parenteral exposure of physicians and patients caused by glove perforation during ophthalmic surgery, gloves were analyzed after 125 procedures. Gloves were collected from all surgical team members (surgeon, assistants, scrub nurse, and circulating nurse). The rate of glove perforation was significantly lower for the surgeon, 0.3% (one of 303 gloves) than for the assistants, 5% (ten of 202 gloves [P = .001]), scrub nurses, 16% (52 of 326 gloves [P = .0001]), and circulating nurses, 15% (43 of 293 gloves [P = .0001]); similarly, assistants had a significantly lower rate than did scrub nurses (P = .0001) and circulating nurses (P = .001). There was no statistically significant difference in number of perforations on the basis of surgery duration or type of ophthalmic procedure. These findings suggest that the risk of parenteral exposure during ophthalmic surgery is low for the surgeon, and higher for other surgical personnel. We also analyzed additional safety precautions. Further study is warranted to determine the effectiveness of precautions and to guide policy formulation.

INCREASING PREVALENCE of the acquired immunodeficiency syndrome (AIDS) has engendered serious concern among physicians and the public about the risks of transmission during medical or dental procedures.[1] The wisdom, ethics, and necessity of widespread testing for the human immunodeficiency virus (HIV) have been extensively debated.[1,2] To date, only one focus (with five cases) of dentist-to-patient transmission has been documented,[1] whereas at least 15 cases of HIV infection in health care workers, contracted through occupational exposure, have been documented.[3]

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From the Doheny Eye Institute, and Department of Ophthalmology, University of Southern California School of Medicine, Los Angeles, California.

Reprint requests to Paul P. Lee, M.D., Doheny Eye Institute, 1450 San Pablo St., Los Angeles, CA 90033.

To formulate a sound policy governing physician-to-patient disclosure, specific data should be acquired. The risk, as well as the mechanism, of intraoperative parenteral exposure to blood from the provider should be determined and precautions to decrease or eliminate such exposure should be investigated. After such information is known, and current knowledge of the rate of actual infection from a given number of exposures is considered, a more informed decision can be made.

Exposure between physicians and patients is most likely during invasive procedures and during trauma stabilization in the emergency room. Given the current use of protective barrier devices, most notably the use of gloves, exposure cannot occur without a breach in that barrier. Furthermore, for physician exposure, there must be a breach in the integrity of the physician's integument, and for patient exposure, there must be an additional step of parenteral exposure to the physician's blood, either directly by seepage through the break in the barrier and then a break in the patient's skin, or indirectly through the instrument or object that breached the protective device and the physician's skin. Although HIV has been found in human tears,[4] no case of transmission by tears has ever been documented.

Ophthalmic surgery involves little bleeding and no sharp objects except for surgical instruments. Irrigating fluid is collected so that it does not run onto the floor or the surgical team. The use of waterproof gowns, masks, and boots, as well as the use of a microscope for most surgery, effectively isolates the surgeon (and thus the patient) from routes of exposure other than glove perforation.

Recent studies have identified glove perforation rates of 17% to 57% in various surgical subspecialties, not including ophthalmology.[5-11] In a 1984 study of ophthalmic surgery in Japan,[12] a rate of 4% to 6% was identified, whereas a recently published abstract, limited to the gloves of ophthalmic surgeons, described a 15% perforation rate.[13] We studied ophthalmic surgical procedures at the Doheny Eye Institute to further describe and quantify intra-

operative exposure to potentially infectious fluids among members of the surgical team and, indirectly, the potential exposure of patients.

Methods

Data collection—From 125 procedures, 1,124 gloves were collected for the study (303 from the surgeons, 202 from the assistants [not all cases had an assistant], 326 from the scrub nurses, and 293 from the circulating nurses). Before the initiation of this study, the circulating nurses were asked to change their usual routine and wear sterile gloves. At the conclusion of the procedures, all gloves were collected by one of us (P.P.) and were evaluated for both gross and hidden perforations. The nursing staff was informed that all gloves should be saved for a study, but the purpose of the study was not disclosed to minimize the possibility that practices might be changed by the study. Because some personnel preferred the hypoallergenic (brown) gloves (Becton Dickinson, Franklin Lakes, New Jersey) over the traditional (white) gloves (Baxter, Valencia, California), a control pair of each type of glove was obtained each day. These 100 gloves were opened and immediately tested for perforations, without previous use; no perforations were detected, which is below the accepted standard for quality assurance (1.5% perforation rate) as designated by the American Society for Testing and Materials.[14]

Gloves that had been contaminated and changed intraoperatively were included in the study. There was no known instance of gloves being changed by the surgeon because of a suspected puncture wound; information on this possibility was not obtained for the assistant or nurses. In the few cases in which a team member wore double gloves, both pairs were tested for perforations and were included in the data analysis.

All cases were performed in the operating suites at the Doheny Eye Institute in Los Angeles, California. The study included both inpatient and outpatient modes of surgery, but did not include any procedures performed in an outpatient office.

Testing for perforations—All gloves were examined initially for gross tears, which were defined as those occurring at the base of the glove and extending distally in a triangular or crescentic pattern. Such tears were assumed to have occurred while putting on or taking off the gloves, and were considered too conspicuous to have gone unnoticed and introduced into the operative field. On this basis, gloves with gross tears (of which there were ten) were excluded from the analyses. After initial inspection, all gloves were distended by filling with a standard volume (500 ml) of water and firmly squeezing. All microperforations were then recorded by number per glove.

Before the study, this method of identifying micropunctures was validated by puncturing three of six gloves with a single pass of a needle attached to a 10-0 nylon suture to ensure that leakage would be detected by a masked observer.

Statistical analysis—The data were evaluated by using both the number of glove perforations (glove perforation rate) and the number of procedures in which perforation occurred (case perforation rate). Each of these was examined separately. Differences between subspecialties, team members, locations of perforations, glove types, and duration of procedure were examined by chi-square analysis. Before analysis, procedures were categorized by duration of surgery as follows: group 1, 0 to 60 minutes (51 procedures); group 2, 61 to 120 minutes (48 procedures); and group 3, more than 120 minutes (26 procedures). The difference in puncture rate between types of gloves was further investigated to control for differences between team members using the Cochran-Mantel Haenszel test. The significance level used for all tests was .05.

Results

At least one glove was perforated by a member of the surgical team during 64 of the 125 procedures, for a case perforation rate of 51%. When analyzed by team members, however, the rates of perforation differed significantly between surgeons, 0.8% (one of 125 procedures) and assistants, 10% (nine of 91 procedures [$P = .008$]), scrub nurses, 31% (39 of 125 procedures [$P = .0001$]), and circulating nurses, 22% (27 of 125 procedures [$P = .0001$]) (Table 1). The difference between assistants and scrub nurses ($P = .0001$) and circulating nurses ($P = .006$) was also significant.

Case perforation rates among subspecialties were as follows: cornea, 42% (16 of 38 cases); glaucoma, 48% (13 of 27 cases); oculoplastics,

TABLE 1
GLOVE PERFORATION RATE AND CASE PERFORATION RATE BY TEAM MEMBER

	NO. OF PERFORATIONS	NO. OF GLOVES	GLOVE PERFORATION RATE (%)	CASES OF PERFORATION*	TOTAL NO. OF CASES PER TEAM MEMBER	CASE PERFORATION RATE (%)
Surgeon	1	303	0.3	1	125	0.8
Assistant	10	202	5.0	9	91	10.0
Scrub nurse	52	326	16.0	39	125	31.2
Circulating nurse	43	293	14.7	27	125	21.6
Total	106	1124	9.4	64	125	9.4

*A given case can count only once toward the total number of cases.

55% (18 of 29 cases); and retina, 56% (15 of 27 cases) (Table 2). There was no statistically significant difference in case perforation rates among subspecialties (P = .66) or duration of procedure (P = .39) for the team as a whole or for surgeons alone among subspecialties (P = .36).

Of the 1,124 gloves, 106 had a perforation, for an overall rate of 9.4%. There were seven gloves with more than one perforation.

When analyzed by team members (Table l), surgeons, 0.3% (one of 303 gloves) had a statistically significant lower rate of glove perforations than did assistants, 5% (ten of 202 gloves [P = .001]), scrub nurses, 16% (52 of 326 gloves [P = .0001]), and circulating nurses, 15% (43 of 293 gloves [P = .0001]). Similarly, assistants had a significantly lower rate than did scrub nurses (P = .0001) and circulating nurses (P = .001). The 95% confidence interval for the rate of glove punctures in surgeons was 0% to 1.0%, whereas that of the assistants was 2.0% to 7.9%.

The differences in glove perforation rate between the subspecialty procedures of cornea (11% [32 of 297 gloves]), glaucoma (7% [16 of 237 gloves]), oculoplastics (11% [28 of 260 gloves]), and retina (9% [26 of 285 gloves]) were not statistically significant (P = .33). Duration of procedure was not associated significantly with glove puncture rate for any team member, although the relationship for scrub nurses approached significance (P = .07) (Table 3). There was no significant difference by subspecialty procedure when analyzed by specific team members.

The difference between perforation rates in brown gloves (12.9% [34 of 263 gloves]) and white gloves (8.4% [72 of 861 gloves]) was significant (P = .03). Further investigation showed that the perforation rates for scrub nurses for brown and for white gloves were 17.7% (28 of 158 gloves) and 14.3% (24 of 168 gloves), respectively; and for the other team members the rates were 6.3% (seven of 111 gloves) and 6.9% (47 of 687 gloves), respective-

TABLE 2
GLOVE PERFORATION RATE AND CASE PERFORATION RATE BY SUBSPECIALTY

	NO. OF PERFORATIONS	NO. OF GLOVES	GLOVE PERFORATION RATE (%)	CASES OF PERFORATION*	TOTAL NO. OF CASES	CASE PERFORATION RATE* (%)
Cornea	32	297	10.8	16	38	42.1
Glaucoma	16	237	6.8	13	27	48.2
Oculoplastics	28	260	10.8	16	29	55.2
Retina	26	285	9.1	15	27	55.6
Total	106†	1,124†	9.4	64	125†	51.2

*Defined as cases in which there was at least one puncture in one glove of the surgeon, assistant, scrub nurse, or circulating nurse.

†Four cases are included in the total number but are excluded from the subspecialty data because they were procedures involving two subspecialties.

TABLE 3
GLOVE PERFORATION RATE AND CASE PERFORATION RATE BY SUBSPECIALTY AND BY TEAM MEMBER

TEAM MEMBER	NO. OF PERFORATIONS	NO. OF GLOVES	GLOVE PERFORATION RATE (%)	CASES OF PERFORATION	TOTAL NO. OF CASES	CASE PERFORATION RATE (%)
Cornea						
Surgeon	0	77	0	0	38	0
Assistant	0	42	0	0	20	0
Scrub nurse	17	88	19.3	3	8	37.5
Circulating nurse	15	90	16.7	8	38	21.1
Glaucoma						
Surgeon	0	62	0	0	27	0
Assistant	3	50	6.0	3	23	13.0
Scrub nurse	7	67	10.5	6	27	22.2
Circulating nurse	6	58	10.3	5	27	18.5
Oculoplastics						
Surgeon	1	67	1.5	1	29	3.5
Assistant	4	49	8.2	3	22	13.6
Scrub nurse	9	81	11.1	9	29	31.0
Circulating nurse	14	63	22.22	7	29	24.1
Retina						
Surgeon	0	81	0	0	27	0
Assistant	3	54	5.6	2	22	9.1
Scrub nurse	17	76	22.4	9	27	33.3
Circulating nurse	6	74	8.1	6	27	22.2

ly. When this difference between scrub nurses and the other team members was considered, there was no significant difference in perforation rates between the two types of gloves ($P = .58$). In other words, the seeming disparity between white and brown gloves was caused by a relative preference for brown gloves among the group with the largest number of punctures—scrub nurses (49% [52 of 106 total punctures]) as opposed to a strong preference for white gloves among those with lower rates (surgeons and assistants, particularly).

Discussion

The risk of exposure of ophthalmologists to blood-borne diseases while performing ocular surgery in an operating room appears to be low. There was a 0.33% rate (one of 303 gloves) of surgeon glove perforation (and a 0.80% case perforation rate [one of 125 cases] for surgeons) in this study. The rate of perforation was higher for assistants, scrub nurses, and circulating nurses.

The low rate of surgeon glove perforation is not unexpected, as there are no sharp instruments in the operative field except those wielded by the surgeon, and there are no sharp edges, such as broken bone, except in certain oculoplastic cases. The only uncertain element is the passing of instruments between the surgeon and the assistant or the scrub nurse. If surgical methods were modified slightly, glove perforations might occur less frequently.

Possible modifications include the use of a no-touch rule,[15,16] the use of deliberate well-choreographed movements between team members, and the use of instrument-to-instrument methods for passing needles. The no-touch rule calls for an instrument never to be handled by more than one team member at a time.[16] When being passed between team members, instruments are placed down in a neutral zone that consists of a tray or mat before being picked up by the next team member. This reduces the risk posed by unchoreographed movements between team members. If the area for placing instruments were magnetic, it might also prevent instruments from falling to the ground, and possibly prevent injuries from

team members reflexively reaching out to grab falling sharp instruments.[15] Also, with increasing use of laser and ultrasonic cutting devices, surgeons will have less frequent contact with blood and tissue.[16] The instrument-to-instrument method entails the use of forceps and needle holders for loading and unloading needles and the use of forceps or a needle holder to advance needles through tissue. At no time is an ophthalmic needle handled directly by a gloved hand. Given the side-cutting nature of many needles, an instrument-to-instrument technique should minimize inadvertent perforations. It is hoped that such measures would decrease the frequency of glove perforations.

We detected a lower rate of surgeon glove perforations than a recently published study, also limited to ophthalmology, which described a rate of 15%.[13] This higher rate may be explained by the testing of each glove by more than one method, including some methods that were more rigorous than ours. Our method of study was similar to that in a 1984 Japanese study of ophthalmic surgery.[12]

Although the control gloves in our study had no perforations, previous studies have found that 2% to 7% of sterile surgical gloves tested immediately after opening of the package had perforations.[5,13] Thus, the one incident of perforation of a surgeon glove in our study may not have resulted from an actual perforation, since this is below the defect rate set for the manufacture of gloves.[13] Even if the perforation were real, the 95% confidence interval suggests that the rate of surgeon glove perforation is less than 1%.

The high rate of perforations for the circulating nurses, 15% (43 of 293 gloves), may suggest that gloves can be torn or perforated by nonpuncture mechanisms. In particular, moving of equipment, twisting of lids, and opening of packages may lead to tearing of the glove. It may also mean that additional precautions need to be taken during disposal of sharp objects. Our circulating nurses do not directly handle unguarded sharp objects before or during their use for patients.

The rates of perforation for assistants, 5% (ten of 202 gloves), and for scrub nurses, 16% (52 of 326 gloves), however, were higher than that for the surgeon, but were consistent with levels described in a 1984 Japanese study.[12] In that study, the incidence of holes in the gloves of assistants ranged from 1.7% to 4.1%, whereas that of nurses ranged from 10% to 11%. It is not altogether surprising that assistants have a higher rate of perforation than do the actual surgeons, since they generally do not control the sharp objects and have their hands and fingers near the operative field, in a position to be stuck. A recent study (not limited to ophthalmic surgery) found that, among perforations with a known cause, a free gloved hand (that is, not holding a sharp instrument) in the operative field was the most likely to be perforated.[17] Also, some assistants help the scrub nurse in various functions, such as loading needles onto forceps, which might further increase the risk of puncture or tearing of the glove.

The high rate of perforation among scrub nurses, however, is more difficult to explain. Some scrub nurses act as assistants for certain procedures, thereby increasing the risk of being stuck by a sharp object near the operative field. The passing of sharp objects between the surgeon and nurse is of major concern, particularly since standard practice is to point the sharp object away from the surgeon—and thus toward the scrub nurse. Additionally, the scrub nurse is asked to perform functions that place shearing stresses on the gloves, such as opening packages or twisting two halves of a sterile instrument together. These nonpuncture mechanisms may have been especially important in our study. Toward the end of a procedure, the scrub nurse begins to clean the tray and surgical area to minimize turnaround time for the next case, which can increase the chances of similar nonpuncture events. Thus, some of the recorded perforations may not be related to mechanisms in the operative field at all. Finally, it is the nursing staff that is expected to dispose of sharp objects after a procedure; in operating suites today, where a quick turnover is expected, careful attention may not always be accorded to precautions. When combined, these factors may account for the higher rate of perforations among scrub nurses.

These findings have implications for surgeons, nurses, and patients. For the health care team, the findings show that the risk of parenteral exposure to viral disease is small for the surgeon, but higher for the nursing staff. Although we did not examine inner and outer gloves separately when double gloves were worn, previous studies have demonstrated that perforation of inner gloves in other surgical specialties is significantly less when double gloves are worn.[5-7,18] Why this occurs is uncertain. It could conceivably represent elimination

of those cases in which glove perforation is caused by mechanisms other than direct penetration by sharp objects. Beck[19] found that, although double-gloving is effective, requiring manufacturers to strengthen gloves might yield even more protection. Even if stronger gloves result in diminished tactile sensation, measures such as texturing the outside of gloves (like our own skin) could compensate for the difference. The use of a thimble or selective reinforcement of glove fingertips has also been advocated.[9,10,19,20]

The more daunting concern to patients is the risk of contracting HIV (or hepatitis B) from the surgeon or other members of the surgical team. From the mechanics of HIV transmission, it is clear that the protective barrier must first be breached and that the health care provider's blood be introduced parenterally into the patient. Thus, the risk of transmission from the provider to the patient in the surgical setting can be no higher than is the risk of a breach of the sterile barrier. When the additional steps needed to introduce the virus into the patient are added, the breach must be major (to reach the provider's blood), and unrecognized so that the glove is not changed or the instrument replaced. As such, the rate of patient exposure to the blood of a provider is bound to be less than the rate of perforation. Not all glove perforations may be caused by penetration with a sharp object. Furthermore, even after exposure, although the rate of actual infection is not known, it is estimated to be exceedingly low.[21,22] One author estimates the risk of transmission from a surgical team member to a patient to be one in 21 million per hour of surgery.[21] Conversely, the transmission from an HIV-positive patient to a health care worker is estimated to be higher, about 0.4% for each percutaneous exposure.[23,24]

The Centers for Disease Control and the American Medical Association do not support the concept of creating a list of exposure-prone services. Further commentary has suggested that even a risk of exposure lower than being struck by lightning may not be acceptable to the public as far as HIV is concerned.[25] Although many authorities support voluntary physician testing for HIV,[25] issues surrounding this are unsettled.

Much of the debate about current infection control procedures focuses on the respective roles of universal precautions[26] and HIV screening. As a single method, the use of universal precautions appears to have several advantages over HIV screening. Universal precautions protect both the patient and health care workers,[23,27] and the protection extends to infectious agents other than HIV.[23,27] Also, universal precautions can be used in the emergency setting, where there is no time to wait for HIV test results,[23,27] and they avoid the socioeconomic pitfalls of dealing with HIV-positive labels.[27] Disadvantages of universal precautions are the additional cost of extra equipment and training, lack of compliance by health care workers, and the reality that universal precautions do not offer 100% protection, especially against injuries from sharp objects.[27]

Human immunodeficiency virus screening does not offer 100% protection either. Because of the lag time between infection and seroconversion, HIV-negative results sometimes provide a false sense of security.[16,23,27] Questions about who should be tested (patients only vs patients and health care workers), the frequency of testing, and the expense of testing and follow-up must all be considered.[23,27] Also, false-positive individuals would incur extra medical costs and, more importantly, face the current stigma of being HIV-positive.[27] Proponents of HIV screening argue that knowledge of HIV-positive status would allow for special infection control procedures or more strict adherence to standard procedures. However, there is evidence that knowledge of a patient's HIV-positive status does not improve precautionary practices by health care workers.[5,27] Also, such measures would already be in place if precautions were adhered to universally.

Studies of preventable exposures to blood and body fluids estimate that as many as 74% of injuries would be prevented by adherence to universal precautions.[5,20,28,29] Implicit in this figure is that 26% were essentially unavoidable despite the use of current universal precautions.[28] The debate about whether limitations of universal precautions can be used to justify HIV screening or only the use of selective HIV testing will surely continue. The use of HIV testing in selected cases, as opposed to mass screening, seems to be justified in the hope that it will improve worker compliance with universal precautions.

We know of two studies that have specifically examined the impact of universal precautions on health care worker behavior.[23,30] One, a survey based on the behavior of health care workers before and after universal precautions training, found a decrease of 51% in blood exposures per year, and a similar decrease of

annual exposures to all body fluids.[28] The study concluded that compliance with universal precautions significantly reduced but did not eliminate the risk of exposure. Another study found low compliance among house officers caring for trauma victims in an emergency setting.[30] Strict universal precautions were adhered to in only 16% of cases, including a compliance rate of only 11% in cases when HIV was suspected. The study found a higher rate of compliance (62% of cases) after universal precautions packs (consisting of gloves, gowns, and the like) were placed in patient care areas. Certainly, universal precautions can be cumbersome in certain situations, especially in emergency rooms, and compliance will sometimes be a problem. It is hoped that increased commitment to universal precautions by hospital administrators and health care workers will decrease parenteral virus exposures. Certainly, universal precautions should already be near optimal levels in operating suites.

In our study, only one surgeon glove had an unrecognized perforation, the cause of which was unknown. Given the rate of perforation caused by manufacturing defects of 1.5% allowed by the American Society for Testing and Materials,[14] this perforation may not have occurred intraoperatively. Additional monitoring may be helpful, but, in this study, the rate of surgeon glove perforation was less than 1%.

The rate was higher for surgical assistants and nurses, but the routine use of double-gloving and greater attention to precautions and intraoperative techniques (such as instrument-to-instrument methods of handling needles by nurses) may significantly lower perforation rates. Unfortunately, in our study, the rate of double-gloving was too small to be valid for statistical analysis. Further investigation is needed to determine the effectiveness of these interventions and to quantify the rate of unrecognized perforation among nurses and assistants. There are data to suggest that the rate of unrecognized perforations is high when comparing intraoperative reporting of perforations to actual postoperative testing of gloves for microperforations,[5,6] and it may be useful if future studies take this into account.

We recommend the use of universal precautions as the primary method for infection control. The use of double gloves, which appears to be increasing among our personnel, should be encouraged. We also recommend the use of selective HIV testing, as well as other tests (such as testing for hepatitis B), rather than the use of mass HIV screening.

The risk of transmission of HIV cannot be totally eliminated in any interaction between two individuals. One could postulate that HIV-infected individuals would wipe their faces, get saliva or tears on a hand, and introduce it (and HIV) into an open wound on an acquaintance's hand by shaking it. Although extremely unlikely, this is not theoretically impossible. Thus, as a matter of policy, we cannot totally eliminate the risk of HIV transmission in our society unless we are to adopt certain measures unacceptable to most individuals.[31]

This study suggests that the rate of unsuspected glove perforations for surgeons during ophthalmic surgery is less than the expected rate of manufacturing defects for surgical gloves. As such, physicians and patients should be reassured that the risk is low, lower than our ability to detect a difference compared to manufacturing standards. The higher perforation rates for nurses and assistants suggest the need for additional investigation.

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Intraocular Lens Power Calculations for Multifocal Intraocular Lenses

Jack T. Holladay, M.D., and Kenneth J. Hoffer, M.D.

We performed calculations for anterior and posterior chamber intraocular lenses, determining the necessary power for emmetropia and 3 diopters of myopia for various axial lengths and corneal powers. Our results demonstrate that to achieve an effective add of 3.00 diopters at the spectacle plane (reading distance of 33 cm), the fabricated add (labeled add) on an intraocular lens must vary from 3.3 diopters for an anterior chamber lens in a patient with a flat cornea, to 5.1 diopters for a posterior chamber lens in a patient with a steep cornea. For most patients, targeting for an effective add of 3 diopters is appropriate, but factors such as availability of fabricated adds from the manufacturer and unusual patient requirements for near vision, may alter this target. We reviewed alternatives with monofocal lenses, such as monovision and compound myopic astigmatism.

Intraocular lens power calculations have been refined to the point that, with third-generation formulas such as the Holladay and associates,[1] Sanders-Retzlaff-Kraff/T,[2] and Olsen, Thim, and Corydon[3] formulas, the limiting factor in prediction accuracy is the precision of the preoperative measurements, not the formula. Third-generation formulas use the axial length and keratometry readings to predict the position of the intraocular lens within the eye, whereas second-generation formulas such as the Binkhorst II, Hoffer II, and Sanders-Retzlaff-Kraff II, use only the axial length to determine the position of the lens. First-generation formulas, such as the Binkhorst I, Hoffer I, and the Sanders-Retzlaff-Kraff I, use a constant in all eyes for a specific intraocular lens and make no adjustment in the position of the lens within the eye as a function of axial length or keratometry readings. Third-generation formulas have been shown to be the most accurate,[1-3] particularly in unusual eyes (axial length less than 22 mm or greater than 25 mm or keratometry readings less than 40 diopters or greater than 47 diopters), and are available on most new ultrasonic biometry instruments. These third-generation formulas are gradually becoming the standard of care.[1-3]

The introduction of multifocal lenses has created another variable in intraocular lens power calculations by adding one or more focal points to the primary focal point of the intraocular lens. With these lenses, the surgeon must not only choose a desired refraction for distance but also choose an effective add or preferred reading distance. Unfortunately, the effective add desired by the surgeon and the actual fabricated add (labeled add) necessary on intraocular lenses are not only different, but are not related by a constant.

We studied the factors that determine the relationship between the effective add and the fabricated add (labeled add) on intraocular lenses. Additionally, we provide a rationale for choosing the appropriate distance power and the proper fabricated add for multifocal intraocular lenses. We compared these choices to alternatives with traditional monofocal intraocular lenses.

Material and Methods

We compared optical defocus (depth of field) characteristics for monofocal and multifocal intraocular lenses (Figure). Although optical differences exist in each of the multifocal intraocular lenses currently manufactured, the defo-

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From Hermann Eye Center, Department of Ophthalmology, University of Texas Medical School at Houston, Houston, Texas (Dr. Holladay); and Jules Stein Eye Institute, Department of Ophthalmology, University of California at Los Angeles, Los Angeles, California (Dr. Hoffer).

Reprint requests to Jack T. Holladay, M.D., Hermann Eye Center, Hermann Hospital, 6411 Fannin St., Houston, TX 77030.

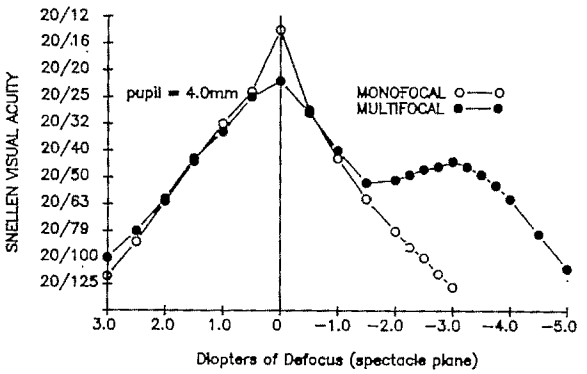


Figure (Holladay and Hoffer). The defocus curves for a monofocal lens (open circles) and multifocal lenses (solid circles) are shown. The areas under the curves to the right of zero represent the range of vision between distance and near. All multifocal lenses can be characterized by this multifocal curve by modifying the height of the peaks and the depth of the valley.

cus characteristics can be closely approximated by slightly adjusting the peaks and valleys of the multifocal curve. For the purposes of intraocular lens power calculations, these differences are not important.

To determine the effect of the axial length, keratometry readings, and the position of the lens within the eye on the necessary fabricated add to achieve a specific reading distance of 33 cm, a series of power calculations were performed using the Holladay and associates formula.[1] We determined the intraocular lens power necessary to achieve emmetropia, as a function of axial length and keratometry readings, for a posterior chamber lens (Table 1) and for an anterior chamber lens (Table 2). Because the posterior chamber lens is closer to the retina than an anterior chamber lens with all else equal, the posterior chamber lens must be stronger to exert the necessary convergence power. In general, the more posterior the lens in the eye, the greater the required lens power necessary to achieve emmetropia.

To determine the necessary intraocular lens power to achieve a reading distance at the typical 33 cm, we simply recalculate the necessary intraocular lens power for a postoperative desired refraction of −3.00 diopters at a spectacle vertex of 12 mm. The difference between the intraocular lens power to achieve emmetropia and a −3.00-diopter spectacle refraction is the fabricated add necessary to be added to the emmetropic lens power. The fabricated add values, as a function of axial length and keratometry readings, were determined for a posterior chamber lens (Table 3) and for an anterior chamber lens (Table 4).

We found that the fabricated add must be increased with increasing axial length, increasing keratometry readings, and the more posterior the lens location behind the cornea (Tables 3 and 4). Also, we found that the increasing axial length has the least effect on the fabricated add, whereas the increasing keratometry readings have a slightly greater effect, and the position of the lens within the eye is the most important factor. Optically, the axial length has no direct effect on the change in fabricated add, only a secondary effect of third-generation formulas that increase the anterior chamber depth proportional to the axial length. No change in the fabricated add was demonstrated in our previous study[4] that used the Hoffer I formula, which did not adjust the position of the lens within the eye on the basis of axial length or keratometry readings.

The smallest fabricated add to achieve a 33-cm reading distance was 3.3 diopters for an anterior chamber lens in a short eye with a flat cornea (Table 4) and the largest was 5.1 diopters for a posterior chamber lens in a long eye with a steep cornea (Table 3). The ratio of the fabricated add to the effective add ranged from

TABLE 1
EMMETROPIC INTRAOCULAR LENS POWER (DIOPTERS) FOR POSTERIOR CHAMBER LENS*

KERATOMETRY READING (DIOPTERS)	AXIAL LENGTH (MM)		
	21.5	23.5	29.5
38.5	32.7	26.1	9.8
43.5	27.3	20.4	3.1
48.5	21.4	14.1	−5.1

*Surgeon Factor = 1.35 and A-constant = 118.2.

TABLE 2
EMMETROPIC INTRAOCULAR LENS POWER (DIOPTERS) FOR ANTERIOR CHAMBER LENS*

KERATOMETRY READING (DIOPTERS)	AXIAL LENGTH (MM)		
	21.5	23.5	29.5
38.5	28.6	23.0	8.8
43.5	23.7	17.8	2.7
48.5	18.4	12.2	−4.5

*Surgeon Factor = −0.20 and A-constant = 115.5.

TABLE 3
FABRICATED ADD (DIOPTERS) ON POSTERIOR CHAMBER LENS* TO ACHIEVE +3.00-DIOPTER EFFECTIVE ADD AT SPECTACLE VERTEX OF 12 MM

KERATOMETRY READING (DIOPTERS)	AXIAL LENGTH (MM)		
	21.5	23.5	29.5
38.5	3.7	3.8	3.9
43.5	3.9	4.1	4.3
48.5	4.2	4.6	5.1

*Surgeon Factor = 1.35 and A-constant = 118.2.

TABLE 4
FABRICATED ADD (DIOPTERS) ON ANTERIOR CHAMBER LENS* TO ACHIEVE +3.00-DIOPTER EFFECTIVE ADD AT SPECTACLE VERTEX OF 12 MM

KERATOMETRY READING (DIOPTERS)	AXIAL LENGTH (MM)		
	21.5	23.5	29.5
38.5	3.3	3.4	3.5
43.5	3.5	3.7	3.9
48.5	3.7	4.0	4.4

*Surgeon Factor = −0.20 and A-constant = 115.5.

1.10 to 1.70, with nominal values of 1.37 for the posterior chamber lens and 1.23 for the anterior chamber lens. Because this ratio is not a constant, formulas that use a refraction factor to determine the ametropic lens power from the emmetropic lens power are not accurate. In short, multiplying a constant (for example, 1.5), times the desired refraction and adding this value to the emmetropic lens power, only introduces a marked error in the result. The refraction factor does not depend on the intraocular lens power, but is primarily a function of the position of the lens within the eye and the corneal power.

Discussion

Choosing the appropriate monofocal intraocular lens power for distance—The defocus curve for monofocal intraocular lenses (Figure)[5,6] demonstrates the vision at various distances when the distance peak is exactly at plano. We have previously discussed the proper choice of monofocal intraocular lens power in detail.[7] The four major factors are as follows:

1. Always choose a desired refraction in the operated-on eye that will be within two diopters of the unoperated-on eye to avoid intolerable anisometropia. The exceptions are if the second eye will be operated on almost immediately after the first eye or if the patient can wear a contact lens to compensate for the anisometropia.

2. If emmetropia is the desired postoperative refraction, then most surgeons target for −0.25 diopter or −0.50 diopter because, at best, only 50% of the patients will be within 0.50 diopter of the desired refraction. The slightly myopic target increases the probability that the patient will have some real distance at which they can have the best vision without spectacles (Figure). When the error is on the hyperopic side there is no real distance at which the patient can see in perfect focus without spectacles.

3. Some authors[8] have recommended a target of −0.75 diopter and leaving the patient with 0.75 diopter of astigmatism, creating a mild compound myopic astigmatism. This compound myopia gives the patient a multifocal effect using Sturm's conoid and allows patients to have approximately 20/40 to 20/50 visual acuity from distance to near with a 3-mm pupil and no spectacles. In dim light, however, as the pupil enlarges, the vision decreases and spectacles are required at all distances.

4. Some authors[9] have recommended monovision in which one eye is targeted for −0.50 diopter and the other for −1.50 diopters. Of these patients, 60% have been reported not to need spectacles. The results depend less on pupil size because the patient actually has two clear focal distances.

Choosing the appropriate multifocal intraocular lens power for distance—All multifocal lenses can be represented by variations of the defocus curve (Figure).[6] For example, a perfect bifocal lens would have a deeper valley between the two peaks. If the design of the intraocular lens emphasizes the clarity of the distance image, the distance peak will be slightly higher than the near peak. A perfect, continuous multifocal lens would induce equal vision from distance to near, by reducing the height of the peaks and raising the valley. It is important to recognize that one part of the curve cannot be raised without lowering the curve in some other part. This relationship occurs because rays are borrowed from one focus and placed at another.

BIFOCAL INTRAOCULAR LENSES—Bifocal intraocular lenses have two discrete focal points by design, one for distance and one for near. The

bifocal design can be either diffractive or refractive and is intended to provide the patient with good distance vision and good reading vision. The ideal result for most patients is plano for distance and a second point of clear focus at a 33-cm reading distance. This would be achieved by performing the intraocular lens calculations for plano and −3.00 diopters (Tables 1 through 4). The power necessary for plano would be the base power of the intraocular lens, and the difference in the intraocular lens power necessary to achieve −3.00 diopters and the base power for emmetropia would be the additional power or the fabricated add (labeled add) on the intraocular lens. We found that the fabricated add ranges from 3.3 diopters for an anterior chamber lens in a short eye with a flat cornea, to 5.1 diopters for a posterior chamber lens in a long eye with a steep cornea (Tables 3 and 4).

With bifocal lenses, targeting for a slightly myopic target would also directly affect the add. If the patient ends up with −0.50 diopter for distance, the effective add will become +3.50 diopters and the reading distance will move in from 33 cm (13 inches) to 28.5 cm (11 inches). This distance may be too close for comfortable reading and other near tasks, such as working at a desk. We therefore recommend choosing the exact intraocular lens power and fabricated add that is calculated to achieve plano and −3.00 diopters.

Unfortunately, most manufacturers only make fabricated adds in one or two powers, for example, +4.00 diopters and +4.50 diopters. The surgeon must simply choose the fabricated add that comes closest to that determined by the intraocular lens calculation. Asking patients where they prefer to hold reading material may also influence the choice between two fabricated adds, in which case choosing the weaker power would be appropriate for patients who like to hold material further away (40 cm or 16 inches).

CONTINUOUS MULTIFOCAL LENSES—Calculating adds for the continuous multifocal lenses (Array lenses, Allergan Medical Optics, Irvine, California, or other aspheric lenses) is treated similarly to that for the bifocal lens, but for a different reason. The continuous change in these lenses from distance to near provides vision at the intermediate range, as well as distance and near (raises the valley and lowers the peaks). Just as the bifocal lens had to sacrifice some image contrast to achieve two focal points, the continuous multifocal lens also must sacrifice some contrast at distance and near to achieve clearer vision at the intermediate distances.[6] The ideal situation occurs when the distance focus and the near focus of this continuous change are located at real distances, that is, between plano and −3.00 diopters.

An error of 0.50 diopter in the hyperopic direction would move the near point further away but have little effect on the distance vision because the distance peak is flatter and not as sensitive to change. Conversely, a 0.50-diopter myopic error would reduce the distance vision, but have little or no effect on the near vision because the near peak is flatter. For this reason, using plano for the distance target refraction and −3.00 diopters for the near increases the probability of a successful result.

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Results of Late Surgery for Presumed Congenital Cataracts

Kenneth W. Wright, M.D., Laurie E. Christensen, M.D., and Barbara A. Noguchi, M.D.

We reviewed the results of cataract extraction and visual rehabilitation in 76 eyes of 47 infants and children with presumed congenital cataracts who were first seen after they were 10 months old. Eighteen patients underwent surgery for unilateral cataracts, including five patients with persistent hyperplastic vitreous, five with posterior lenticonus, one with a nuclear cataract, six with posterior subcapsular cataracts, and one with a lamellar cataract. Of these 18 patients, seven (39%) attained a visual acuity of 20/60 or better, one (6%) had a visual acuity of 20/100, and ten (60%) had a visual acuity of 20/200 or worse. Twenty-nine patients (62 eyes) underwent bilateral cataract extraction. The visual acuity could be measured in 22 patients (44 eyes). Visual acuity improved to 20/60 or better in 32 eyes (73%), was between 20/70 and 20/150 in 11 eyes (25%), and became worse than 20/200 in one eye (2%). Results were good in patients with persistent hyperplastic primary vitreous, posterior lenticonus, and bilateral cataracts.

OUR CLINICAL EXPERIENCE and previous reports[1,2] have shown that some children with presumed congenital cataracts show substantial improvement even when surgery is performed late after the critical period of visual development (after 10 months of age). Previous results substantiate these findings. Owens and Hughes[3] found that 37.8% of patients with bilateral total congenital cataracts achieved a visual acuity of 20/70 or better, and François[4] had similar results. We evaluated the visual prognosis of children who underwent late surgery for presumed congenital cataracts and identified preoperative clinical signs that could help predict visual outcome.

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From the Department of Ophthalmology, University of Southern California School of Medicine and Division of Ophthalmology, Childrens Hospital of Los Angeles, Los Angeles, California (Dr. Wright); Oregon Health Sciences University, Portland, Oregon (Dr. Christensen); and Department of Ophthalmology, Tulane University, New Orleans, Louisiana (Dr. Noguchi).

Reprint requests to Kenneth W. Wright, M.D., Division of Ophthalmology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd., Los Angeles, CA 90027.

Patients and Methods

Charts from 211 consecutive children who underwent unilateral or bilateral lensectomies between 1980 and 1988 at Childrens Hospital of Los Angeles were reviewed. Of these 211 patients, 50 met the inclusion criteria for this study, which included lensectomy after 10 months of age for a presumed congenital cataract. Patients with acquired cataracts secondary to trauma or an identifiable metabolic cause were excluded from the study.

Cataracts are classified as unilateral or bilateral and by their morphologic characteristics.[5-7] Lamellar cataract is defined as a lens opacity that affects the cortical layers outside the nucleus and the Y sutures. Nuclear cataract is defined as an opacity located between the Y sutures in the nuclear part of the lens.[7] Lamellar cataracts were included, even though they typically develop after birth, as these opacities often surround the lens nucleus, giving the appearance of a nuclear cataract as well as the impression of being congenital.[5] Six patients had bilateral cataracts and preoperative nystagmus, including four with nuclear cataracts and two with total cataracts.

The ages of the patients at the time of surgery ranged from 10 months to 15 years (mean, 5 years 1 month). Most extractions were performed by one of us (K.W.W.), but four other staff surgeons also operated on patients. The average follow-up was 2½ years for patients with a unilateral cataract, and two years one month for those with bilateral cataracts. All patients were followed up for at least six months. Forty-seven patients were included in the study (18 with unilateral cataracts and 29 with bilateral cataracts).

In preverbal children, cataract extraction was indicated if the opacity blocked at least 3 mm of

the central visual axis, distorting both retinoscopy and direct ophthalmoscopy. In older children, a linear visual acuity of 20/70 or worse was an indication for surgery, except for one patient who had surgery performed on the second eye with a visual acuity of 20/50 because of decreasing vision.

All patients were treated with a limbal-approach lensectomy with vitrectomy instrumentation.[8] In three patients, the posterior capsule was left intact and a secondary YAG laser capsulotomy was performed one month postoperatively. In the remaining patients, a posterior capsulotomy and anterior vitrectomy were performed as part of the primary procedure.

Aphakia was managed with flexible-wear contact lenses in all cases. Patients with unilateral aphakia were treated with occlusion therapy of the fellow eye.

Visual acuity was measured using either single or linear optotype testing with Allen pictures, illiterate E, or Snellen chart. In patients too young to cooperate with optotype visual acuity testing, visual acuities were estimated by the child's ability to fixate and to follow objects. The postoperative visual acuities recorded were obtained during the most recent follow-up visit. Postoperative visual rehabilitation consisted of combinations of contact lenses, spectacles, and patching regimens for amblyopia.

Results

Unilateral cataracts—Of 18 eyes with unilateral cataracts, five were caused by persistent hyperplastic primary vitreous, five were caused by posterior lenticonus, two were nuclear, six were posterior subcapsular, and one was lamellar (Table 1). Postoperatively, all 18 patients were able to cooperate with visual acuity testing with optotypes. Seven patients (39%) attained a visual acuity of 20/60 or better, one patient (6%) had a visual acuity of 20/100, and 11 patients (58%) had a visual acuity of 20/200 or worse.

Strabismus—Of the 18 patients with unilateral cataracts, 11 had preoperative strabismus. The absence of strabismus was a good prognostic sign, with four of the eight nonstrabismic patients (50%) achieving a visual acuity be-

TABLE 1
PATIENTS WITH UNILATERAL CATARACTS

PATIENT NO.	TYPE OF CATARACT	AGE AT SURGERY	PREOPERATIVE VISUAL FINDING	POSTOPERATIVE VISUAL ACUITY	FOLLOW-UP
1	Persistent hyperplastic primary vitreous	10 mos	Poor fixation	20/40 Allen	3 yrs 4 mos
2	Persistent hyperplastic primary vitreous	1 yr 6 mos	Poor fixation	14/30 Allen	2 yrs 8 mos
3	Persistent hyperplastic primary vitreous	1 yr 11 mos	No fixation	10/30 Allen	7 mos
4	Persistent hyperplastic primary vitreous	2 yrs 10 mos	Poor fixation	5/200 illiterate E	1 yr 4 mos
5	Persistent hyperplastic primary vitreous	4 yrs 4 mos	3/30 Allen visual acuity	20/60 Snellen	2 yrs 2 mos
6	Posterior lenticonus	1 yr 9 mos	Poor fixation	4/200 illiterate E	3 yrs 1 mo
7	Posterior lenticonus	3 yrs 1 mo	Light perception	15/30 Allen	6 mos
8	Posterior lenticonus	3 yrs 7 mos	12/30 Allen visual acuity	20/30 Snellen	3 yrs 11 mos
9	Posterior lenticonus	4 yrs 6 mos	1/30 Allen visual acuity	2/30 Allen	7 mos
10	Posterior lenticonus	6 yrs 8 mos	1/200 illiterate E visual acuity	10/200 illiterate E	1 yr 9 mos
11	Posterior subcapsular	10 mos	No fixation	1/30 Allen	3 yrs 2 mos
12	Posterior subcapsular	2 yrs 1 mo	No fixation	1/30 Allen	4 yrs 6 mos
13	Posterior subcapsular	3 yrs 7 mos	No fixation	Light perception	2 yrs 1 mo
14	Posterior subcapsular	5 yrs 9 mos	20/200 illiterate E visual acuity	20/100 Snellen	3 yrs 1 mo
15	Posterior subcapsular	7 yrs	5/200 illiterate E visual acuity	20/200 illiterate E	8 mos
16	Posterior subcapsular	15 yrs 2 mos	20/100 Snellen visual acuity	20/25 Snellen	1 yr 11 mos
17	Nuclear	10 mos	Poor fixation	1/30 Allen	8 yrs 6 mos
18	Lamellar	5 yrs	4/30 Allen visual acuity	20/200 illiterate E	2 yrs 4 mos

tween 20/40 and 20/25. In contrast, only one of 11 patients with strabismus achieved a visual acuity of 20/40. The presence of strabismus did not, however, preclude marked improvement, as the visual acuity in four of the 11 patients with unilateral cataracts and strabismus improved to 20/100 or better.

Unilateral persistent hyperplastic primary vitreous—Of the five patients in this group, four achieved a visual acuity of 20/60 or better. One patient had a poor visual outcome, with a postoperative visual acuity of 20/800, which was secondary to a congenital tractional detachment of the macula.

Posterior lenticonus—Of five patients in this group, two attained postoperative visual acuity of 20/30 (Snellen) and 20/40 (Allen card, Snellen equivalent). The remaining three patients had a postoperative visual acuity of 2/30 (Allen card), 20/400, and 4/200 (illiterate E), respectively.

Unilateral nuclear cataracts—The one patient with a unilateral nuclear opacity had a poor visual outcome of 1/30 visual acuity (Allen card).

Unilateral posterior subcapsular cataracts—Of the six patients in this group, four had postoperative visual acuities of 20/200 or worse, one had a 20/100 visual acuity, and one patient (Patient 16) had a visual acuity of 20/25.

Unilateral lamellar cataracts—The one patient in this group had exotropia and a visual acuity of 4/30 (Allen card) preoperatively; the postoperative visual acuity was essentially unchanged at 20/200 (Snellen).

Bilateral cataracts—Twenty-nine patients underwent bilateral cataract extraction (Table 2). Postoperative optotype visual acuities were recorded from 44 eyes of 22 patients. Visual acuity improved to 20/60 or better in 32 eyes (73%), was between 20/70 and 20/150 in 11 eyes (25%), and became worse than 20/200 in one eye (2%). Using the visual acuity of 20/60 as the criterion for a good visual result, we found that 15 of 22 patients (68%) achieved a good visual acuity in both eyes; two of 22 (9%) achieved a good visual acuity in one eye, but poor visual acuity in the fellow eye; and five of 22 (23%) had poor visual acuity in both eyes.

Seven of the 29 patients were too young to cooperate with postoperative visual acuity testing with optotypes. Five of the seven patients had improved fixation in both eyes, whereas the other two patients showed no change in fixation of either eye postoperatively.

Nystagmus—Four of six patients (Patients 1, 6, 17, 18, 25, and 26; Table 2) with preoperative nystagmus had marked postoperative improvement in visual acuity and marked lessening of the nystagmus. In two of these patients with preoperative nystagmus (Patients 1 and 18), postoperative optotype visual acuity could be obtained. Patient 1 achieved a 13/20 visual acuity by Allen picture cards (approximately 20/50 Snellen equivalent) and Patient 18 had a 20/70 visual acuity by linear Snellen.

Bilateral nuclear cataracts—This group comprised 18 patients with bilateral nuclear cataracts, five of whom had a nuclear cataract in one eye and a total cataract in the fellow eye. Of the 18 patients, 14 (28 operated-on eyes) underwent postoperative optotype visual acuity testing. Visual acuity improved to 20/60 or better in 23 of the 28 eyes (82%), and between 20/70 and 20/150 in five eyes (18%). Visual acuity on an individual patient basis (using the eye with better vision) ranged from 20/150 to 20/20, with 12 of the 18 patients (67%) achieving a visual acuity of 20/60 or better.

Bilateral posterior subcapsular cataracts—Three patients had posterior subcapsular cataracts, including two patients with bilateral posterior subcapsular cataracts and one patient with a total cataract in the fellow eye. Comparison of preoperative and postoperative visual acuities showed marked improvement in each case. The postoperative visual acuity in the eye with better vision was 20/50 (Patient 19), 20/70 (Patient 20), and 20/80 (Patient 21), respectively, for these three patients. One of the patients (Patient 21) had a marked difference in visual acuity, as one eye was amblyopic at 20/200.

Bilateral lamellar cataracts—Three patients had bilateral lamellar cataracts. The visual acuity of all three patients improved postoperatively (20/25 in both eyes in Patient 22, 20/40 in both eyes in Patient 23, and R.E.: 20/70 and L.E.: 20/50 in Patient 24).

Bilateral total cataracts—Bilateral total cataracts were present in four patients, two of whom were able to cooperate with visual acuity testing with optotypes at the last follow-up visit. Postoperative visual acuity in the eye with better vision was 20/30 and 20/120 (Allen card, Snellen equivalent) for these two patients.

Bilateral cerulean (blue dot) cataracts—The one patient with cerulean cataracts was able to fixate and follow light with both eyes preoperatively. This child was able to fixate and follow light postoperatively, but was lost to follow-up after six months.

TABLE 2
PATIENTS WITH BILATERAL CATARACTS*

PATIENT NO.	AGE AT SURGERY		TYPE OF CATARACT		PREOPERATIVE VISUAL FINDING	
	R.E.	L.E.	R.E.	L.E.	R.E.	L.E.
1	1 yr 4 mos	1 yr 4 mos	Nuclear	Nuclear	Poor fixation	Poor fixation
2	1 yr 6 mos	1 yr 6 mos	Nuclear	Nuclear	Fair fixation	Fair fixation
3	1 yr 6 mos	1 yr 6 mos	Nuclear	Nuclear	Fair fixation	Fair fixation
4	1 yr 11 mos	2 yrs 2 mos	Total	Nuclear	Poor fixation	Fair fixation
5	2 yrs	3 yrs	Total	Nuclear	No fixation	Fair fixation
6	4 yrs 3 mos	4 yrs 5 mos	Total	Nuclear	No fixation	Poor fixation
7	4 yrs 5 mos	4 yrs 5 mos	Nuclear	Nuclear	2/30 Allen	5/30 Allen
8	5 yrs 1 mo	5 yrs 1 mo	Nuclear	Nuclear	4/30 Allen	5/30 Allen
9	5 yrs 4 mos	5 yrs 2 mos	Nuclear	Nuclear	20/70 Snellen	20/80 Snellen
10	6 yrs	5 yrs 5 mos	Nuclear	Nuclear	20/100 Snellen	20/400 Snellen
11	6 yrs 8 mos	6 yrs 8 mos	Nuclear	Nuclear	20/200 Snellen	20/200 Snellen
12	6 yrs 8 mos	7 yrs 1 mo	Nuclear	Nuclear	2/200 Snellen	2/200 Snellen
13	8 yrs	6 yrs 10 mos	Nuclear	Nuclear	20/50 Snellen	5/30 Snellen
14	7 yrs 10 mos	8 yrs 1 mo	Nuclear	Nuclear	20/200 Snellen	20/200 Snellen
15	13 yrs 1 mo	8 yrs 6 mos	Nuclear	Nuclear	20/70 Snellen	20/80 Snellen
16	8 yrs 10 mos	9 yrs 10 mos	Nuclear	Nuclear	20/200 Snellen	20/100 Snellen
17	14 yrs 2 mos	14 yrs 2 mos	Nuclear	Total	Hand motions	Light percepton
18	14 yrs 8 mos	14 yrs 6 mos	Nuclear	Nuclear	20/200 Illiterate E	7/200 Illiterate E
19	4 yrs 6 mos	4 yrs 6 mos	Posterior subcapsular	Posterior subcapsular	20/80 Snellen	20/100 Snellen
20	5 yrs 5 mos	5 yrs 5 mos	Total	Posterior subcapsular	Light perception	20/30 Allen
21	8 yrs 4 mos	8 yrs 4 mos	Posterior subcapsular	Posterior subcapsular	10/200 Illiterate E	6/200 Illiterate E
22	6 yrs 1 mo	5 yrs 7 mo	Lamellar	Lamellar	20/200 Snellen	20/100 Snellen
23	6 yrs 6 mos	7 yrs 1 mo	Lamellar	Lamellar	Poor fixation	Poor fixation
24	13 yrs 2 mos	12 yrs 11 mos	Lamellar	Lamellar	20/80 Illiterate E	20/100 Illiterate E
25	1 yr	1 yr	Total	Total	No fixation	Fair fixation
26	1 yr 1 mo	1 yr 1 mo	Total	Total	Poor fixation	Poor fixation
27	2 yrs 3 mos	2 yrs 3 mos	Total	Total	Poor fixation	Poor fixation
28	2 yrs 6 mos	2 yrs 6 mos	Total	Total	0/30 Allen	0/30 Allen
29	1 yr 11 mos	2 yrs	Cerulean blue dot	Cerulean blue dot	Fair fixation	Fair fixation

*Patients 1, 6, 17, 18, 25, and 26 had preoperative nystagmus, which decreased postoperatively in Patients 1, 6, 18, and 25.

Discussion

Some patients with unilateral cataracts develop relatively good visual acuity even when cataract surgery was performed after the child was 10 months old. This group with a good visual prognosis included patients with persistent hyperplastic primary vitreous, posterior lenticonus, bilateral nuclear cataracts, lamellar cataracts, and patients without strabismus. The absence of strabismus is a good prognostic sign, as four of eight patients with unilateral cataracts and essentially straight eyes achieved a visual acuity between 20/40 and 20/25.

Four of five (80%) patients with persistent hyperplastic primary vitreous obtained visual acuities of 20/60 or better. Karr and Scott[9] also found good visual results in patients with persistent hyperplastic primary vitreous. One of their patients who underwent lensectomy and anterior vitrectomy at 10 months of age achieved a 20/50 visual acuity. These good results may be attributed to a faint posterior opacity at birth, which allows development of central fixation. Over time, the opacity increas-

TABLE 2 *(Continued)*
PATIENTS WITH BILATERAL CATARACTS

POSTOPERATIVE VISUAL RESULTS		LENGTH OF FOLLOW-UP	
R.E.	L.E.	R.E.	L.E.
13/30 Allen	13/30 Allen	1 yr 8 mos	1 yr 8 mos
Fair fixation	Fair fixation	6 mos	6 mos
Good fixation	Good fixation	9 mos	9 mos
20/30 Allen	20/30 Allen	2 yrs 8 mos	2 yrs 5 mos
Good fixation	Good fixation	1 yr	1 mo
Good fixation	Good fixation	1 yr 3 mos	1 yr 1 mo
20/20 Snellen	20/30 Allen	4 yrs 3 mos	4 yrs 3 mos
20/100 Snellen	20/50 Snellen	1 yr 6 mos	1 yr 6 mos
20/30 Snellen	20/25 Snellen	1 yr 2 mos	1 yr
20/30 Snellen	20/40 Snellen	1 yr 6 mos	2 yrs 1 mo
20/20 Snellen	20/25 Snellen	1 yr	1 yr
20/25 Snellen	20/30 Snellen	1 yr 5 mos	1 yr 1 mo
20/40 Snellen	20/40 Snellen	10 mos	2 yrs
20/25 Snellen	20/40 Snellen	4 yrs 2 mos	4 yrs 5 mos
20/25 Snellen	20/30 Snellen	3 mos	4 yrs 7 mos
20/20 Snellen	20/30 Snellen	4 yrs	3 yrs
4/30 Allen	4/30 Allen	1 yr 10 mos	1 yr 10 mos
20/70 Snellen	20/80 Snellen	1 yr	1 yr 2 mos
20/50 Snellen	20/50 Snellen	6 mos	6 mos
20/80 Snellen	20/70 Snellen	1 yr 6 mos	1 yr 6 mos
20/80 Snellen	20/200 Snellen	6 mos	6 mos
20/25 Snellen	20/25 Snellen	2 yrs 4 mos	2 yrs 10 mos
20/70 Illiterate E	20/50 Illiterate E	7 yrs 6 mos	6 yrs 11 mos
20/40 Illiterate E	20/40 Illiterate E	2 yrs 7 mos	2 yrs 10 mos
Good fixation	Good fixation	1 yr 10 mos	1 yr 10 mos
Good fixation	Good fixation	6 mos	6 mos
20/30 Allen	20/40 Allen	5 yrs 11 mos	5 yrs 11 mos
5/30 Allen	5/30 Allen	11 mos	11 mos
Fair fixation	Fair fixation	6 mos	5 mos

es and an amblyopia of relatively late onset develops. Persistent hyperplastic primary vitreous presents as a wide spectrum of disease, and patients with retinal involvement have a poor prognosis. The one patient in our study who did not have a marked improvement in visual acuity postoperatively had a congenital peripapillary traction band that extended from the optic nerve stalk to the macula, which caused a macular detachment.

Posterior lenticonus, like persistent hyperplastic primary vitreous, is a condition that is congenital but progressive, often causing minimal distortion of the retinal image at birth.[10,11] Crouch and Parks[10] described 21 patients who underwent cataract extraction for posterior lenticonus; all but two of the patients were first seen after they were 1 year old. The visual acuity in 15 of the 21 patients improved to 20/50 or better postoperatively. The patients with posterior lenticonus in our series also developed relatively good vision. Two of five patients (40%) attained visual acuities equivalent to 20/40 or better.

Unilateral cataracts associated with a relatively poor prognosis include monocular nucle-

ar cataracts, monocular posterior subcapsular cataracts, and cataracts in patients with strabismus. Some of these patients, however, showed marked postoperative improvement. One patient with a posterior subcapsular cataract achieved 20/25 visual acuity, and four of 11 patients (36%) with a unilateral cataract and strabismus achieved a visual acuity between 20/100 and 20/40. We agree with Parks[12] that distinguishing between congenital and acquired cataracts in infants and young children may be impossible. It is difficult, therefore, to predict which children will have irreversible amblyopia and which have the potential for marked visual acuity improvement.

Nuclear opacities indicate a congenital onset and therefore usually have a poor visual prognosis.[7,12,13] The only patient in our study with a unilateral nuclear cataract (Patient 17) had a poor visual result. Patients with bilateral nuclear cataracts, however, did relatively well, with 12 of 18 patients (67%) attaining a visual acuity of 20/60 or better. In patients who achieved visual acuity of 20/60 or better, the nuclear opacities may have been relatively clear during the critical period of visual development, and later progressed. Direct progression of the nuclear opacity was documented in four of the 19 patients in our study who had a good visual outcome. This observation is supported by the results of Bercovitch and Donaldson,[14] who photographically documented the progression of a nuclear cataract.

Nystagmus in a child with bilateral cataracts indicates dense amblyopia and a poor visual prognosis.[12,15,16] Parks[12] described eight patients with nystagmus secondary to congenital cataracts and found that none had a visual acuity better than 20/200 postoperatively. Five of the eight patients, however, were too young to cooperate with optotype visual acuity testing. In our series, four of six patients with bilateral cataracts and nystagmus showed improved visual acuity and lessening of nystagmus postoperatively, with two patients achieving visual acuities of 20/50 and 20/70, respectively. Sensory nystagmus generally indicates a poor prognosis, but the presence of nystagmus in a patient with cataracts does not preclude marked visual improvement. Because cataract extraction is a relatively low-risk procedure, this procedure should be considered for patients with sensory nystagmus who would otherwise be blind.

We do not advocate delay of surgery in infants with visually significant cataracts. The optimum treatment for both monocular and binocular congenital cataracts is early surgery and visual rehabilitation before 2 months of age, preferably within the first few weeks of life.[12,16-22] However, when a child with a unilateral or bilateral cataract is treated after the critical period, the possibility for visual improvement should not be categorically discounted.

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OPHTHALMIC MINIATURE

It is no good asking for a simple religion. After all, real things are not simple. They look simple, but they are not. The table I am sitting at looks simple, but ask a scientist to tell you what it is really made of—all about the atoms and how the light waves rebound from them and hit my eye and what they do to the optic nerve and what it does to my brain—and, of course, you find that what we call "seeing a table" lands you in mysteries and complications which you can hardly get to the end of.

C. S. Lewis, *Mere Christianity*
New York, Collier Books, 1952, p. 46

The Tokyo Metropolitan Home Vision Screening Program for Amblyopia in 3-Year-Old Children

Koji Yazawa, M.D., Junnosuke Suga, M.D., Shigeru Wakita, M.D., Masami Sumitomo, M.D., and Yasuo Uemura, M.D.

In August 1989, the Tokyo Metropolitan Government officially began a vision screening program for children aged 3 years 1 month. A 1988 pilot study of 1,303 children this age disclosed five cases (0.38%) of amblyopia. The home vision test, which uses picture cards of familiar figures, proved to be an efficient and inexpensive method of screening when incorporated into the existing health-check program for 3-year-old children. In the initial eight months of the program, 21,906 children were screened. Of these, 419 children (1.9%) were referred to an ophthalmologist for follow-up, and amblyopia was detected in 41 children (0.19%).

We believe prevention of blindness should begin in the home during early childhood. We developed a home vision test that focuses public attention on vision and encourages children, parents, and grandparents to learn more about eyes. Throughout Japan, extensive use of the Maternal and Child Health Handbook of Japan (Ministry of Health and Welfare, Government of Japan, 1987) has had an important role in decreasing the infant mortality rate to the lowest in the world: 4.8 per 1,000 live births. On reporting a pregnancy, nearly all expectant mothers receive the handbook from their local public health office. Subsequently, the family is notified when to bring the child in for periodic health examinations and vaccinations. Before 1988, vision screening was not addressed in the handbook; however, the newly revised edition recommends eye examinations at the time of general health examinations at the ages of 18 months, 2 years, and 3 years, as well as visual acuity testing at 4, 5, and 6 years of age. Parents now understand the importance of vision screening and are aware of their child's eye examination schedule.

Subjects and Methods

Approximately one month before the scheduled health examination, a home vision test kit is mailed to the parents of 3-year-old children. The health examination takes place when the child is 3 years 1 month old. Parents are instructed to administer the test and bring the results with them to the public health office at the time of their child's appointment. The test kit contains a picture card, instructions, and an answer sheet. Tissue paper and plastic tape are used to patch alternately the eye not being tested. The picture card contains the following four figures: a bird, a fish, a butterfly, and a tulip. These figures correspond to a visual acuity measurement of 20/40 at 2.5 m. The card is cut in four pieces, and the child is shown the figures one at a time. A child who is able to identify three of the four figures correctly is considered to have a visual acuity of 20/40 or better, which we consider normal for this age. A child able to identify only two figures or fewer is considered to have below-normal visual acuity and is referred to an ophthalmologist for further examination. The government covers the cost of initial physician's fees and screening expenses. When a child's responses during the

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From the Department of Ophthalmology, Juntendo University, School of Medicine, Tokyo, Japan (Drs. Yazawa and Wakita); Department of Ophthalmology, Keio University, School of Medicine, Tokyo, Japan (Drs. Suga and Uemura); and Maternal and Child Health Section, Public Health Division, Bureau of Public Health, Tokyo Metropolitan Government, Tokyo, Japan (Dr. Sumitomo).

Reprint requests to Koji Yazawa, M.D., 3-16-2, Shibasaki-cho, Tachikawa-shi, Tokyo 190, Japan.

first test are not reliable, parents are instructed to administer the test again in one month and report the results to the public health office.

This home vision screening program started in August 1989 in the Tama district, a suburb of Tokyo. In 1990, the program was expanded to include the entire city of Tokyo (population, 11,718,720), which includes 113,779 3-year-old children (population figures as of January 1989).

Results

A pilot study of this program was conducted in 1988 (Table 1). Test kits were mailed to the parents of 1,546 3-year-old children along with health examination notices. As a result, 1,331 children (86.1%) attended their examination at 3 years of age. Parents of 1,303 of these children (97.9%) brought the results of the home vision test. While 1,252 children (96.1%) were able to complete the test, 51 children (3.9%) were not. Of those tested, 1,187 children (91.1%) were able to identify three or four figures (visual acuity ≥ 20/40); 30 children (2.3%) could not identify at least three figures and were referred to an ophthalmologist, and 79 children (6.1%) were required to repeat the test in one month. Follow-up testing was canceled in another seven children (0.5%) because of retardation or other difficulties in examining vision. On referral, amblyopia was detected in five children (0.38%). Three children (Cases 1 through 3) had anisometropic amblyopia, one child (Case 4) had refractive amblyopia (high hypermetropic), and one child (Case 5) had strabismic amblyopia (Table 2).

TABLE 1
RESULTS OF HOME VISION SCREENING PROGRAM

	NO. OF CHILDREN	
	1988 PILOT STUDY	OFFICIAL PROGRAM (AUGUST 1989–MARCH 1990)
Size of study		
Notified	1,546	25,217
Attended health examination	1,331	21,906
Brought test results	1,303	21,391
Home vision test		
Total tested	1,303	21,391
Completed test	1,252	20,618
Unable to complete test	51	738
Not reported	0	35
Results		
Total tested	1,303	21,391
Visual acuity normal (≥ 20/40)	1,187	19,860
Visual acuity below normal (≤ 20/50)	30	407
Required follow-up test	79	1,023
Too difficult to evaluate	7	66
Not reported	0	35

The official screening program started in August 1989. The results of the initial eight months of screening (August 1989 through March 1990) were analyzed (Table 1). Parents of 25,217 3-year-old children were sent test kits with the health examination notification. Subsequently, 21,906 children (86.9%) attended their examination at 3 years of age. Parents of

TABLE 2
FIVE CASES OF AMBLYOPIA DETECTED BY HOME VISION TEST (PILOT STUDY)

CASE NO.	NO. OF FIGURES IDENTIFIED*		VISUAL ACUITY					
			WITHOUT REFRACTION		WITH REFRACTION		CYCLOPLEGIC REFRACTION	
	R.E.	L.E.	R.E.	L.E.	R.E.	L.E.	R.E.	L.E.
1	0	3	20/300	20/40	20/200 × +5.00	20/40 × +1.00	+8.00	+4.00
2	0	4	20/400	20/40	20/60 × +5.00	20/40	+5.00	+2.00
3	4	0	20/30	20/400	20/30	20/200 × +5.00	+2.00	+6.00
4	1	0	20/250	20/200	20/200 × +5.00	20/200 × +5.00	+6.00	+6.00
5†	3	2	20/40	20/200	20/30 × +2.50 −0.50 × 180	20/200 × +5.00 −1.00 × 180	+3.50	+7.00 −1.00 × 180

*Out of four figures on picture test card.

†This patient had intermittent esotropia.

21,391 children (97.3%) brought the results of the home vision test. Of these 21,391 children, 20,618 children (96.4%) were able to complete the test, and 738 children (3.5%) were not. The test results disclosed normal visual acuity in 19,860 children (92.8%) and below-normal visual acuity in 407 children (1.9%). Additionally, 1,023 children (4.8%) were required to repeat the test in one month. Of those children referred, 41 were sent to five university hospitals, 120 went to government or private hospitals, and 261 visited private practitioners. The reports from these referrals were collected and analyzed by the Maternal and Child Health Department of the Tokyo Metropolitan Government (Table 3). Forty-one cases (0.19%) of amblyopia and 48 cases (0.22%) of strabismus were reported. This home vision test can detect amblyopia, but it cannot detect strabismus alone; therefore, we ask parents, at the time of the health examination or by questionnaire, if they have noticed any clinical signs of strabismus in their child. If the public health nurse suspects strabismus, the child is referred for further examination. No case of strabismus or amblyopia detected in this program had been previously detected by an ophthalmologist.

Discussion

Picture cards lack the scientific validity of Landolt rings. However, screening cannot occur unless these young children cooperate and play the test game. Over 96% of the children could complete the test and 41 cases of previously undetected amblyopia (nearly 0.2% of those screened) were found, which indicated that this is a satisfactory screening examination for 3-year-old children. In a preliminary study conducted before our pilot study, we discovered that children had an easier time completing the home vision test with pictures vs Landolt rings. A group of 587 children were tested at home with a vision chart that contained pictures and Landolt rings. The four figures from the picture card test were aligned horizontally across the top row of the chart and four Landolt rings were aligned in a row below. At a distance of 2.5 m from the chart, each child was asked to identify the figures and was then also asked to locate the openings of the rings on the chart either by pointing or with the "drive-a-car" method in which the child "steers" a cardboard ring that has an opening and attempts to match the opening of this hand-held ring with the openings of each of the rings on the chart. Of the 587 children tested, 554 (94.4%) were able to complete the picture test, whereas only 379 children (64.5%) were able to complete the test by using Landolt rings.

Other researchers have studied vision in 3-year-old children. Kozaki, Iwai, and Mikami[1] studied the distribution of visual acuity in 168 3-year-old children as part of the child's health examination at the public health office. These researchers found that 78% of those studied had a visual acuity of 20/40 or better, and 22% had a visual acuity of 20/50 or worse. While 31% of the children with a visual acuity of 20/50 or worse required correction, only 1.8% of those with a visual acuity of 20/40 or better required correction. Kanda and Kawase[2] studied the distribution of vision in 91 3-year-old children. In their study, 93% of the children had a visual acuity of 20/40 or better, whereas 6% had a visual acuity of 20/50 or worse. These researchers concluded that a visual acuity of 20/40 or better at 3 years of age is normal.

Our pilot program disclosed amblyopia in 0.38% of the participants, whereas in the first eight months of the ongoing program, amblyopia was found in only 0.19% of those screened. Clearly, this discrepancy requires further research. One of us (K.Y.)[3] used retinoscopy to study refractive errors in 18-month-old children at the public health office. From 1984 to 1986, 4,601 children were examined. Hyperme-

TABLE 3
RESULTS OF 419 REFERRALS
(AUGUST 1989 THROUGH MARCH 1990)

DIAGNOSIS	NO. OF CHILDREN
Amblyopia	41
Anisometropic	24
Refractive	13
Strabismic	2
Form vision deprivation	2
Strabismus	48
Esotropia	27
Exotropia	11
Inferior oblique muscle overaction	7
Not classified	3
Apparent esotropia	28
Refractive errors	187
Normal findings	116

tropic anisometropia greater than +5.00 was found in six children (0.13%) and hypermetropia greater than +5.00 in both eyes was found in 15 children (0.3%). These children are candidates for amblyopia. Therefore, it is reasonable to conclude that home vision screening for 3-year-old children is successful if the detection of refractive and anisometropic amblyopia reaches 0.4%.

To meet the increasing number of referrals generated by the home vision screening program, 200 practicing ophthalmologists have enrolled in the program. Referrals throughout Tokyo are estimated to reach 2,000 annually.

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OPHTHALMIC MINIATURE

Porter did not laugh, however, when Otten took to greasing spectacles in the mess hall. Neither did Calhoun. Otten was quick as a striking snake and when no noncom was looking could flick a fore-finger through the butter and smear it across both lenses of a bespectacled comrade before any protective reflex could be activated. The resultant mess obscured vision until the victim could find hot water and soap, Otten sniggering and pointing for the entire interval. Porter's solution was to quit wearing his glasses. This was not an option for Calhoun, whose lenses were so crafted that they shrank his eyes as effectively as Pygmy head hunters mummified their trophies: he was helpless without them.

Ferrol Sams, *When All The World Was Young*
Atlanta, Longstreet Press, 1991, p. 184

Ocular Hydrofluoric Acid Burns

Roy S. Rubinfeld, M.D., David I. Silbert, M.D., Juan J. Arentsen, M.D., and Peter R. Laibson, M.D.

A 30-year-old man sustained exposure of his eyes, face, and neck involving 4% of body surface area to hydrofluoric acid. He was treated with immediate lavage and topical calcium gluconate. Because free fluoride ions from ocular and facial exposures can form complexes with body stores of calcium and magnesium, the patient was transferred to a burn unit for cardiac and electrolyte monitoring. He was also treated with calcium gluconate skin injections, pulmonary nebulizer therapy, and topical antibiotics and corticosteroids. In another case, a 25-year-old man with less severe exposure to hydrofluoric acid was treated as an outpatient with topical antibiotics, corticosteroids, and cycloplegia. If an ophthalmologist is the first to treat a patient with chemical exposure, the history of hydrofluoric acid exposure must be obtained, and the burn team and other medical specialists must be quickly consulted to avoid potentially fatal complications.

INFORMATION ON OCULAR BURNS caused by hydrofluoric acid is lacking in the ophthalmic literature, despite the relatively high incidence of these burns. A recent study in the United Kingdom showed hydrofluoric acid to be the cause of injury in 50% of acid burns in a large regional burn unit.[1] Its use in industry is widespread and includes applications in petrochemical production, glass making, glass etching, mineral processing, and semiconductor manufacturing.[2-4] More alarming, it is also found in some commercially available cleaning solutions.[4] These factors are important because seemingly benign ocular and facial exposure to hydrofluoric acid can have potentially fatal consequences if unrecognized and untreated.

Hydrofluoric acid is an inorganic acid that takes the form of a colorless gas or a volatile liquid that is miscible in water. It is corrosive and difficult to store. Like most acids, hydrofluoric acid causes an initial burn as a result of the dissociation of hydrogen ions. However, unlike other acids, it causes more insidious damage because of deep penetration of fluoride ions.[5] Although the pH of the burn surface may increase rapidly to normal levels after lavage, deeper tissues may be at great risk for serious injury.

Minimal skin exposure to hydrofluoric acid can cause severe, life-threatening metabolic imbalances because the free fluoride ion forms complexes with calcium and magnesium, thereby depleting body stores of these minerals. Skin exposure involving as little as 8% of body surface area can cause intractable cardiac arrhythmia and death from hypocalcemia.[6] Ocular exposure may denude the corneal and conjunctival epithelium, and cause stromal corneal edema and conjunctival ischemia. Deeper penetration of the fluoride ions may cause delayed opacification of the cornea and necrosis of the anterior chamber structures.[7]

We managed two cases of ocular hydrofluoric acid burns.

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From the Cornea Service (Drs. Rubinfeld, Arentsen, and Laibson), Wills Eye Hospital, Philadelphia, Pennsylvania; and the Center for Sight/Department of Ophthalmology, Georgetown University Medical Center, Washington, D.C. (Drs. Rubinfeld and Silbert). This study was supported in part by the Corneal Research Fund, Philadelphia, Pennsylvania; and by an unrestricted grant from Research to Prevent Blindness, Inc., New York, New York.

Reprint requests to Roy S. Rubinfeld, M.D., Suite 950, 5454 Wisconsin Ave., Chevy Chase, MD 20815.

Case Reports

Case 1

A 30-year-old man was at work operating a compressor-extruder machine that contained hydrofluoric acid. The extruder exploded, knocking the patient's safety glasses off and spraying aerosolized and solid particles of hy-

drofluoric acid in the man's face. He received burns to his forehead, most of the anterior portion of his face (including the conjunctivae of both eyes), and to the anterior portion of his neck, totaling approximately 4% of body surface area. He was immediately taken to an on-site shower where his face and eyes were irrigated copiously with water for ten minutes.

The patient was transferred to a local hospital where his eyes were irrigated with 6 l of 0.9% saline solution. His initial visual acuity was R.E.: 20/20−2 and L.E.: 20/20−3. He was then transferred to Wills Eye Hospital. Physical examination at that time (3½ hours later) showed a visual acuity of R.E.: 20/200 and L.E.: 20/50, as well as bilateral severe eyelid edema and conjunctival chemosis. Mild to moderate limbal conjunctival blanching that involved approximately three fourths of the limbal area was present in the right eye. The left eye had only trace limbal blanching. Excoriated periorbital and nasal skin and devitalized and sloughing corneal epithelium were also present, more severe in the right eye than in the left eye. The patient was treated with instillation of prednisolone acetate 1%, four times a day; gentamicin 0.3%, four times a day; and 0.25% scopolamine, twice a day, to both eyes. Two drops of 1% calcium gluconate solution in unpreserved sterile water were instilled in both eyes every two to three hours. A gel made of 2.5% calcium gluconate in glycerin was applied to the face.

Once the degree of hydrofluoric acid exposure was assessed, the patient was immediately transferred to a regional burn unit. There, under sedation, he received intradermal injections of 10% calcium gluconate to the forehead, eyelids, nose, and malar eminences on the first and second hospital days. A 26-gauge needle was used to administer 10% calcium gluconate at a dosage of 0.5 ml/cm^2 of exposed skin surface. A gel of 25% magnesium sulfate in glycerin was also applied to his face.

On the second hospital day, his sloughing, necrotic conjunctiva was debrided to reduce the fluoride load further and to aid in healing. Calcium gluconate 1% solution in sterile water was instilled in both eyes four times daily during his hospital stay. The patient was discharged on day 5 with a persistent corneal epithelial defect of the right eye. Discharge medications included topical 1% prednisolone acetate, four times a day in the right eye and twice a day in the left eye; 0.3% gentamicin, four times a day in the right eye; 0.25% scopolamine, twice a day in the right eye and four times a day in the left eye; and oral hydroxyzine hydrochloride, 25 mg, four times a day.

In addition to ophthalmic follow-up, medical, pulmonary, otorhinolaryngologic, and rehabilitation consultations were ordered while he was an inpatient in the burn unit. Superficial airway burns were treated with saline nasal spray to keep his upper airways open. A chemical bronchitis was treated with a metaproterenol sulfate nebulizer. Laboratory values including blood gases were normal, except for serum fluoride. Phosphorus, magnesium, and calcium levels were monitored every four hours for 48 hours and remained within the normal range. The patient's skin burn improved steadily, with only superficial epidermal loss. He developed no infections or metabolic imbalances.

Nine days after his acid exposure, at an outpatient visit at the Cornea Service, a 6 × 4-mm epithelial defect of the right cornea was noted. Pinhole visual acuity was R.E.: 20/300 and L.E.: 20/80. The right cornea was hypesthetic and edematous, with moderate Descemet's folds. Subconjunctival hemorrhages were also present. Examination of the anterior chamber disclosed moderate flare and minimal cells. The left eye was well healed and only mild anterior stromal haze was present. The topical medications were continued and bilateral patching at bedtime was initiated. These treatment measures resulted in healing of the persistent epithelial defect within ten days and over a two-month period, the patient's visual acuity improved to R.E.: 20/30−1 and L.E.: 20/20+3. The right cornea remained hypesthetic, and he continued to complain of occasional foreign-body sensation. There was some residual anterior corneal scarring of both eyes. Intraocular pressure remained between 14 and 16 mm Hg throughout treatment.

Case 2

A 25-year-old man had hydrofluoric acid sprayed in his right eye. He was treated in an emergency room and released. Five days later, he was admitted to the Wills Eye Hospital Cornea Service with a foreign-body sensation in his right eye, and an inferior 4 × 5-mm corneal erosion. Marked inferior bulbar and tarsal conjunctival injection, and chemosis and subconjunctival hemorrhages were also present. The left eye was normal. His visual acuity was R.E.: 20/60 and L.E.: 20/15. His right eye was patched with erythromycin, sulfacetamide

sodium, and prednisolone acetate ointments and scopolamine 0.25% drops. Calcium gluconate solutions were not used. Three days later, the corneal epithelium was intact, although slightly elevated and irregular. There was a slight stromal haze in the right eye and mild ciliary flush. His visual acuity in the right eye had improved to 20/30+2. After this visit he was lost to follow-up.

Discussion

Despite the increasing use of hydrofluoric acid in industry and even in some household products, there is a lack of information on hydrofluoric acid burns in the ophthalmic literature. In addition to a few anecdotal reports, two cases of hydrofluoric acid burns of the eye have been described,[7,8] and in these studies, it is unclear whether the injury was caused by some other caustic substance, hydrofluoric acid alone, or a combination of agents. The burns in our two patients were caused exclusively by hydrofluoric acid.

Essential elements of the treatment of ocular and periocular exposure to hydrofluoric acid include prompt recognition of the cause of the burn, and early water lavage to remove most of the hydrofluoric acid. Irrigation with 1% calcium gluconate, after initial saline solution lavage, has been suggested to help form complexes with the free fluoride ions[3,5,9]; however, the efficacy of this treatment has not been proven. McCulley and associates[7] experimented with the use of topical and subconjunctival administration of various fluoride binders in rabbit eyes. Treatment with topical magnesium oxide or magnesium sulfate ointment, irrigation with 0.2% benzethonium chloride, or 0.05% benzalkonium chloride and subconjunctival injection with 10% calcium gluconate were highly toxic to normal rabbit eyes. Subconjunctival injections of magnesium chloride and calcium chloride caused additional damage to burned eyes. Additional irrigation beyond the initial lavage with water, isotonic sodium chloride, or magnesium chloride resulted in increased incidence of corneal ulceration in rabbits with hydrofluoric acid burns.[7] The use of calcium gluconate drops and debridement were not studied.

The eye may be affected by liquid or airborne exposure to hydrofluoric acid.[10] Damage includes epithelial sloughing, and deep penetration of the fluoride ions into the corneal stroma. Hydrofluoric acid can also cause extensive conjunctival ischemia.[7] Like other inorganic acids, hydrofluoric acid causes an initial corrosive burn because of the pH effect. The severity of this initial damage is considerably less than the damage from equimolar concentration of sulfuric or hydrochloric acid. However, the penetration of the fluoride ions (which can continue for several days if untreated) can result in cellular death and tissue necrosis.[3] Consistent with our Case 2, delayed corneal damage four days after exposure has been described in a patient who was admitted to an emergency room five days after injury.[8] McCulley and associates[7] found that in rabbits exposed to various strengths of hydrofluoric acid, the degree of conjunctival ischemia and corneal penetration depended on the strength of the acid. With skin exposure to concentrations less than 20%, the clinical symptoms of the burn may be delayed up to 24 hours, leading to confusion as to the cause of the burn.[8]

Neither of our two patients experienced life-threatening complications. In Case 1, the patient received prompt and appropriate ocular and systemic medical attention. Without this, his clinical result may not have been so favorable. In Case 2, the exposure was far less extensive.

Hydrofluoric acid exposure can have fatal consequences if unrecognized. Exposure to 7 ml of anhydrous hydrofluoric acid (hydrofluoric gas) can bind all the free calcium in a 70-kg adult man, causing potentially fatal hypocalcemia.[3] One death caused by hypocalcemia and cardiac arrest from a facial burn of less than 2.5% of body surface area has been described.[11] Because of the high vascularity of the face, the uptake of fluoride ions is much greater with a facial burn than with a burn to other areas of the body.[3] Facial exposure is also more likely to place a patient at risk for injury from inhalation of aerosolized hydrofluoric acid. This can cause increased systemic absorption, airway obstruction, and pulmonary edema. A case of pulmonary thrombosis resulting in death after respiratory exposure to hydrofluoric gas has been described.[12] Facial exposure to hydrofluoric acid thus places a patient at greater risk of serious systemic complication than would a similarly sized exposure of other body areas.

General treatment of hydrofluoric acid burns to the skin should begin with immediate flushing of the exposed body part with cool water

for 15 to 20 minutes. Contaminated clothing should be removed and cautiously disposed of because it is a potential source of hydrofluoric gas. After lavage, topical treatment can be initiated with calcium gluconate gel, 2.5%, to the exposed skin surfaces to precipitate the fluoride ions and create insoluble salts. Such a gel can be prepared by mixing 3.5 g of calcium gluconate with a 140-g tube of water-soluble surgical lubricant.[10] A gel made of 25% magnesium sulfate in glycerin can also be used for this purpose. High molecular weight quaternary amines, benzalkonium chloride, and benzethonium chloride have also been suggested by some authorities.[10] The patient should then be transferred to the emergency department of a hospital with a specialized burn unit.

Hydrofluoric acid burns are extremely painful. Absence of pain itself is a good indicator of the efficacy of treatment. If pain persists for more than 45 minutes, subcutaneous injections of 5% to 10% calcium gluconate may be given to bind fluoride ions in deeper tissue planes.[8,10] Intra-arterial calcium gluconate infusion has been described as a treatment for digital hydrofluoric acid burns.[5]

The patient must be monitored for systemic effects. If inhalation is suspected, thoracic radiography and arterial blood gas analysis should be performed. The patient should receive humidified oxygen, and nebulizer treatments with 2.5% calcium gluconate may be appropriate. Electrolytes must be closely monitored to prevent potentially lethal electrolyte abnormalities. Continuous cardiac monitoring is required with special attention to lengthening of the QT interval, a sign of hypocalcemia. Finally, the physician must watch for clinical signs of pulmonary edema.[8,10]

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Stray Light in Radial Keratotomy and the Influence of Pupil Size and Straylight Angle

Henk G. N. Veraart, M.D., Thomas J. T. P. van den Berg, Ph.D., Jan K. IJspeert, M.Sc., and Oscar Lopes Cardozo, M.D.

Glare is a major sequela of the radial keratotomy procedure. We used the straylight meter to measure intraocular light scatter, which is the cause of glare, in eyes after radial keratotomy. This apparatus uses a direct compensation method to assess the amount of intraocular light scatter. Nineteen patients were tested. Nine individuals served as controls. The mean postsurgery time was 60 months. The influence of the number of radial incisions, the pupil size, and the angle of light entering the eye were evaluated with the straylight meter. The results showed straylight values for normal pupil size (mean, 4 mm) to be statistically significantly higher (P = .0044) only for the smallest angle of light deflection studied (3.5 degrees). For dilated pupils (mean, 8 mm), straylight values were statistically significantly higher (P = .00005) for all three angles of light deflection studied. The number of incisions showed no statistically significant relationship to straylight values. Average stray light values were increased by a factor of 1.4 for 4-mm sized pupils and 2.0 for 8-mm sized pupils. There was an overlap in straylight values between the patient population and the control population.

COMPLICATIONS OF RADIAL KERATOTOMY have been described by a number of studies.[1-11] Glare is one of the most frequently mentioned sequelae of this procedure. Although not blinding, glare actually or potentially can reduce vision. The severity of glare seems to diminish markedly during the first six months after radial keratotomy and to subside gradually thereafter. The major problem in assessing the importance of glare is the difficulty in judging the patient complaints objectively.

In 1985 the Prospective Evaluation of Radial Keratotomy Study Group used the Miller/Nadler Glare Tester for glare testing in their population.[3] With this glare tester no statistically significant increase in glare at one year after radial keratotomy was found despite subjective complaints of glare in 212 of 407 patients (52%). At the four-year examination of this group of patients no glare testing was performed.[4] The Prospective Evaluation of Radial Keratotomy Study Group stated at that time that the extent and severity of night glare were unknown, but that many patients saw radiating lines around focal light sources after radial keratotomy. In 1989 Rashid and Waring[5] stated that the majority of individuals who have had radial keratotomy see a starburst pattern at night, which, although not disabling, did cause some patients to curtail driving at night.

In 1987 Applegate and associates[12] developed a modified, two-channel tachistoscope in an effort to quantify objectively the amount of glare in eight eyes after radial keratotomy. They found large glare effects in all eyes as well as large interindividual variation. The postoperative time to glare testing in this series was short (three to seven months) and pupil size was not taken into account.[13] Atkin and associates[14] measured the effects of glare on contrast sensitivity in patients after radial keratotomy. Their results showed a decrease in contrast sensitivity in the presence of a glare source. They demonstrated greater contrast sensitivity losses in those patients whose pupil diameters were larger.

Glare testing is an indirect method to assess intraocular light scatter. The techniques used in most commercially available glare testers are

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From the Department of Ophthalmology, Lievensberg Hospital, Bergen op Zoom, The Netherlands (Drs. Veraart and Cardozo); and The Netherlands Ophthalmic Research Institute and the Laboratory of Medical Physics and Informatics of the University of Amsterdam, Amsterdam, The Netherlands (Dr. van den Berg and Mr. IJspeert).

Reprint requests to Thomas J. T. P. van den Berg, Ph.D., Laboratory of Medical Physics and Informatics, University of Amsterdam, Meibergdreef 15, 1105 AZ Amsterdam, The Netherlands.

based on the effect on visual function of a bright light source at some angular distance. Visual function includes visual acuity and contrast sensitivity. The parameters that these tests measure are related only indirectly to the amount of intraocular stray light and results may be influenced by criterion changes, adaptation changes, and malfixations.

Current glare testers do not seem to be sensitive enough to measure the increase in glare that occurs after radial keratotomy despite many patients being bothered by this phenomenon. Using a direct method of determination, we used the straylight meter to measure accurately the amount of light scattering in eyes after radial keratotomy. Care was also taken to control pupil size during the tests.[15]

Patients and Methods

Thirty-eight eyes of 19 radial keratotomy patients were tested. All the tests were performed by one of us (H.G.N.V.) in the outpatient department at the Lievensberg Hospital. Short travel distance to the clinic was the basis for patient selection. Patient age varied from 23 to 44 years (mean, 34 years). The mean postoperative time was 60 months (range, 25 to 79 months). Uncorrected and best-corrected monocular visual acuities were recorded in a 6-m lane. A projected Snellen chart with consistent background illumination was used. Uncorrected visual acuity ranged from 20/100 to 20/15 with an average of 20/22.5. Best-corrected visual acuity ranged from 20/20 to 20/15. Anterior and posterior segment examination showed no signs of any previous or present abnormality in any of the eyes examined.

All surgical procedures were performed by the same surgeon (O.L.C.), with the patient under local anesthesia. Optical zone diameters varied from 3.0 to 4.5 mm. Freehand incisions were made with a diamond knife, starting at the edge of the optical zone and terminating at the tip of the corneal vascular arcade. The number of radial incisions varied from four to 32. After the procedure, a topical neomycin-polymyxin-dexamethasone ophthalmic solution was administered for one month.

Nine individuals served as a control population. Uncorrected visual acuity in 18 eyes ranged from 20/200 to 20/15. The mean visual acuity was 20/22.5. Best-corrected visual acuity ranged from 20/20 to 20/15. Age ranged from 20 to 35 years (mean, 26 years). The mean age of the radial keratotomy patients was greater than that of the controls. This, however, did not bias the measurements as normal population studies[16] indicate an insignificant 4% (0.02 log unit) increase between ages 26 and 34 years.

We used the straylight meter to measure intraocular light scatter.[15] This instrument uses a direct compensation method[17] to assess the amount of forward scattered light. This scattering of light is responsible for retinal contrast reduction and subsequently glare. In this technique[17] no thresholds are measured. An eccentric light source and a central light patch flicker in counterphase at a frequency of 8 Hz. The eccentric light source consists of a ring of point light sources while the central patch is fixed. The angular radius of the ring can be set to give angles (Φ) of light incidence into the eye of 3.5, 10, or 28 degrees.

The patient fixates on the unilluminated central patch while one of the eccentric light rings is set to flicker. Subjectively, the central patch is also perceived to be flickering. This is as a result of intraocular scattering of the light from the eccentric source. This flicker impression can be extinguished by varying the luminance of the counter modulated, flickering, central patch. The luminance modulation L, which eliminates or minimizes the flicker perceived centrally, corresponds directly to the amount of intraocular stray light. In this way the effect of intraocular light scatter is directly compensated.

By using this method it is not necessary to correct refractive errors as long as the one-degree radius central patch can be discriminated. Fixation errors are of minor importance because the spatial relation between the eccentric light sources and the central patch are not influenced by malfixations. Criterion or adaptation changes are also irrelevant.[15] The condition of the retina is not important, as long as it can detect an 8-Hz flicker. The retina is therefore used as a null instrument, its sensitivity being unrelated to the values obtained. Straylight values are expressed as so-called straylight parameters[15]: $\Phi^2 * L/E$. E is illuminance modulation on the eye by the straylight source. Test-retest error is in the order of 0.1 log unit standard deviation.[15]

The tests were performed by one of us. Both eyes of each patient were measured, starting with the right eye, the other eye being covered by the patient's hand. The patients adjusted the luminance of the central patch themselves, and

the left eye was used as a control of interobservation differences. These observations were not used in the statistics, only the results from the right eyes. No corrective spectacles or contact lenses were used during the tests. Three measurements were made for each of the three angles of eccentric light incidence. Pupil diameters were measured before and after each test run. After an initial series of measurements, a drop of tropicamide 0.5% ophthalmic solution was administered to the right eye. While the pupil was dilating repeated test runs were performed, using all three incident angles, until the pupil was fully dilated. Test runs were then performed on both eyes again, the right pupil being fully dilated and the left of normal size as a control for reproducibility. After straylight testing, subjects were asked to answer four standard questions to assess their subjective glare experiences. Each positive answer was counted as 1 and a total score of 0 to 4 resulted.

Results

For the control population, straylight values measured with the normal pupil size (range, 3 to 5 mm; mean, 4 mm) were compared with the values from dilated pupils closest to 8 mm (range, 7 to 9 mm; mean, 8 mm) (Fig. 1). No statistically significant difference between the results for the two pupil diameters was found. The curve was in accordance with results from a large normal population study.[16]

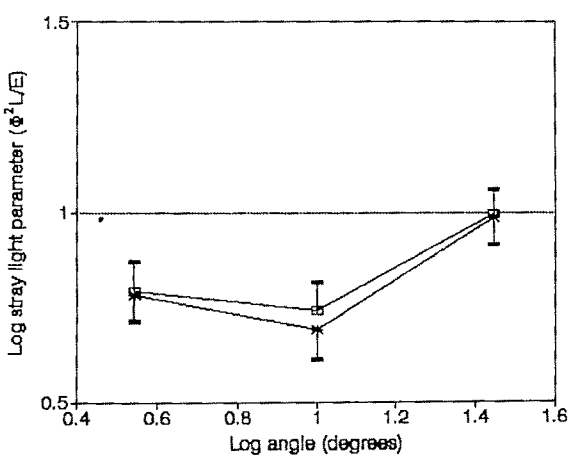


Fig. 1 (Veraart and associates). Straylight parameter values and standard error of the means as a function of light incidence angle for the controls. There is no difference between normal pupils (squares) and 8-mm sized pupils (stars).

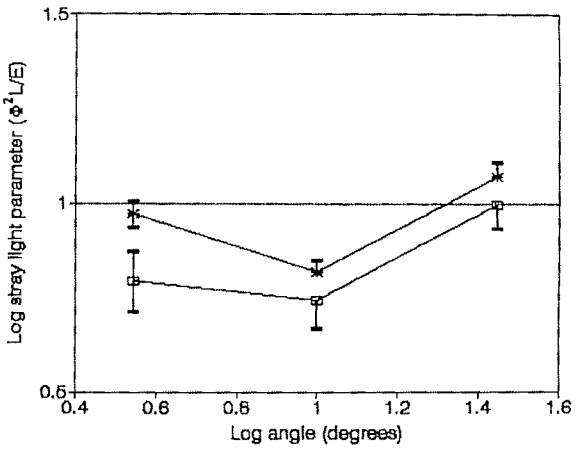


Fig. 2 (Veraart and associates). Straylight parameter values and standard error of the means as a function of light incidence angle for normal pupil sizes. A small increase in straylight parameters exists for the radial keratotomy population (stars) as compared to the control population (squares).

A comparison between the radial keratotomy group and the control group when tested with undilated pupils was made (Fig. 2). The mean straylight values from the radial keratotomy group were higher for all angles of incident light but the difference was statistically significant only for incident light at 3.5 degrees of eccentricity ($P = .0044$).

Both populations with dilated, 8-mm wide pupils were compared (Fig. 3). The radial keratotomy group showed statistically significantly higher straylight values at all angles of incident light ($P = .00005$). This increase was in the order of a factor of 2. This increase was equal to the average increase found in 70-year-old, healthy individuals with visual acuity of 20/20.[16]

The relationship between straylight values and the number of incisions in 8-mm pupils was also noted (Fig. 4). Plotted was the mean of log straylight parameter for the three angles. The correlation coefficient between log straylight parameter and log number of incisions (radial keratotomy patients only) was 0.37 ($P = .06$). The subjective score of glare experienced by the subjects increased with the increase in mean straylight parameter but this increase was not statistically significant.

Discussion

We attempted to measure intraocular light scattering as the physical basis for glare com-

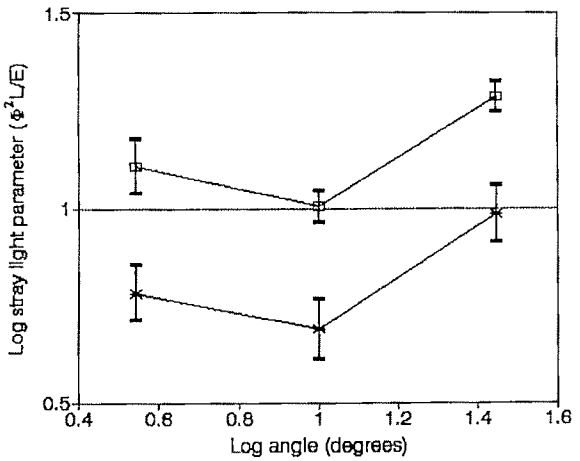


Fig. 3 (Veraart and associates). Straylight parameter values and standard error of the means as a function of light incidence angle for 8-mm sized pupils. A clear increase in straylight parameters exists for the radial keratotomy population (squares) as compared to the control population (stars).

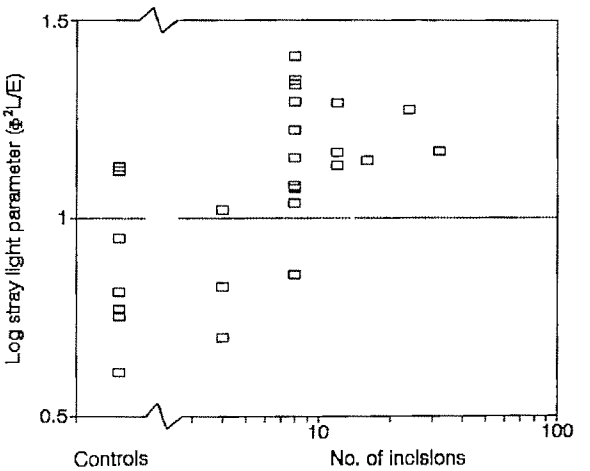


Fig. 4 (Veraart and associates). The data points (squares) show the relationship between the average log straylight parameter values for the three angles of incident light in 8-mm sized pupils and the number of radial incisions.

plaints.[18] The straylight meter is a sensitive instrument and is able to detect small differences in intraocular light scattering. Fixation errors and changes in criteria or adaptation are unimportant. The results showed that there was a small but definite increase in straylight values in radial keratotomy subjects. The mean increase was a factor of 1.4 (0.15 log unit) in eyes with 4-mm sized pupils and a factor of 2 (0.3 log unit) for 8-mm sized pupils. This increase must be the result of scattering of light in the cornea.

Little correlation between the number of incisions and straylight values was found. This suggests that the scattering of light is caused more by changes in corneal tissue not involved in the cuts rather than by the actual incisions themselves. This is confirmed by the increase in straylight values found in undilated pupils. Conversely, the larger increase found for 8-mm sized pupils suggests that corneal tissue adjacent to the incisions also scatters an abnormal amount of light. It should also be kept in mind that the importance of stray light from the more peripheral zones of the cornea is reduced by the Stiles-Crawford effect.[19] Therefore, the true physical increase in stray light with an increase in pupil diameter may be much greater. Consider that the stray light measured is the functionally relevant quantity for foveal (and photopic) vision. Since the Stiles-Crawford effect is much less pronounced peripherally (and scotopically), the importance of stray light may be greater at night than might be expected on the basis of these measurements.

In interpreting these results it must be kept in mind that light scattering appears in every eye, and it is a normal phenomenon that people are blinded by oncoming headlights, or the sun at dawn and at dusk. People are accustomed to these troublesome experiences and only a few complain spontaneously. There are, however, great differences in stray light values among normal individuals. Among young people the differences generally relate to differences of eye coloration.[20] Straylight values increase with age for healthy noncataractous eyes.[16] The differences within the normal population[17] are of the same order as the mean increase found in radial keratotomy patients. There is, therefore, a marked overlap between radial keratotomy patients and the normal population. Yet, complaints do occur more often in radial keratotomy patients. Apart from the actual increase in straylight values found in these patients, it seems probable that radial keratotomy patients find the difference in light scattering bothersome before and after the procedure. The increase in straylight values constitutes some loss of visual function in radial keratotomy patients. On the average, the increase in stray light is limited and some subjects may be aware of this postoperative effect, whereas others may not be.

Radial keratotomy could, therefore, be the cause of decreased visual function in working conditions that require extreme visual perfor-

mance, especially with large pupils, for example for airline pilots and sea captains. This visual degradation may or may not be perceived as such by different individuals or they may elect not to mention the glare effects of a radial keratotomy. In general, especially with normal pupils, these effects are slight and will not be an important long-term postoperative complication. Nevertheless, an absence of glare complaints after a radial keratotomy procedure does not necessarily mean that the individual does not have significantly impaired visual function as a result of intraocular light scatter. We believe it may be important to measure stray light as a factor in visual function in certain individuals before deciding that individual's job fitness.

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Photorefractive Keratectomy for Severe Postkeratoplasty Astigmatism

Mauro Campos, M.D., Lars Hertzog, B.S., Jenny Garbus, B.S., Martha Lee, Ph.D., and Peter J. McDonnell, M.D.

We performed cylindric corneal ablations with the excimer laser on 12 patients to correct severe, disabling astigmatism after keratoplasty. In some patients, an additional ablation was performed to correct myopia. Patients were followed up for an average of eight months (range, six to 14 months). Uncorrected visual acuity improved in nine patients, and nine of the 12 patients had a decrease in refractive cylinder at last follow-up. The mean preoperative refractive cylinder was 7.0 ± 3.6 diopters, which decreased to a mean of 3.1 ± 2.6 diopters at one month (P = .0003) and 4.3 ± 2.9 diopters at last follow-up (P = .03). Keratometric astigmatism decreased from 7.5 ± 3.9 diopters preoperatively to 5.2 ± 3.9 diopters at the last follow-up (P = .001). Mean spherical equivalent was reduced from −7.4 ± 4.2 diopters preoperatively to −3.3 ± 4.4 diopters postoperatively (P = .003). Postoperative corneal haze, when present, did not reduce visual acuity. Excimer laser superficial keratectomy thus appears to be safe when used for postkeratoplasty ametropia, although substantial regression may limit its effectiveness in some patients.

THE OUTCOME of penetrating keratoplasty has improved with advances in microsurgical techniques, more stringent criteria for selection of donor material, and better postoperative care. The visual recovery after such a surgical procedure, however, is often adversely affected by severe postoperative astigmatism despite a clear graft.[1] Several surgical options have been described for correction of this postoperative astigmatism, but the results remain relatively unpredictable.[2-6]

Photorefractive keratectomy with the 193-nm excimer laser is under investigation as an option for treatment of refractive errors and for excision of superficial cornea opacities. To correct myopia, a radially symmetric surgical procedure is performed with greater ablation depth centrally than peripherally[7-9]; to excise superficial corneal opacities, a uniform ablation depth is used.[10] A nonradially symmetric approach to tissue ablation with flattening of the steep meridian for correction of corneal astigmatism has been described in plastic spheres, animals, and human eyes.[11,12] We used this technique for correction of severe astigmatism after keratoplasty.

Patients and Methods

The laser used was a 193-nm argon-fluoride excimer laser (Twenty-Twenty, VISX, Inc., Sunnyvale, California). The detailed methods of this procedure have been described previously.[11,12] To correct astigmatism, a large-diameter laser beam is passed between a set of parallel blades. The separation between the blades is controlled by computer (with the slit opening during the procedure), and the resultant variable slit is used to control the laser delivery much as the iris diaphragm is used for correction of myopia. As in laser treatment to correct myopia, 240 steps are used. By using the slit, the resultant corneal flattening is only in the meridian perpendicular to the long axis of the slit (mechanical axis); no refractive change is intended along the mechanical axis. Alignment of the mechanical axis with the astigmatic axis of the patient is achieved by rotating the slit

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From the Doheny Eye Institute, and Department of Ophthalmology, University of Southern California School of Medicine, Los Angeles, California. This study was supported by a grant from the Autry Foundation, Los Angeles, California (Dr. McDonnell).

Reprint requests to Peter J. McDonnell, M.D., Doheny Eye Institute, 1450 San Pablo St., Los Angeles, CA 90033.

mechanism with computer control. Ablations were performed by using a fluence of 160 mJ/cm^2 and a repetition rate of 5 Hz.

To calibrate the laser, we performed toric ablations in polymethylmethacrylate blocks and the induced cylinder was measured with a lensometer, as described previously.[11]

Informed consent was obtained from all patients after the nature and risks of the procedure were explained. To be eligible for the study, the patients must have had demonstrable improvement in visual acuity when corrected with the phoropter, but we did not require that they be correctable to 20/20. It was common for visual acuity to be correctable with contact lenses to a level one or two lines better than with spectacles, a consequence of a component of irregular astigmatism. Twelve patients were included in this study. None of these patients could tolerate contact lenses or the high cylindric correction needed in spectacles. Other surgical options were offered to the patients. This investigational procedure is under a protocol approved by the Food and Drug Administration and the Institutional Review Board of the University of Southern California. Preoperative examinations included slit-lamp microscopy and photography for documentation. An experienced examiner performed refraction, keratometry, ultrasonic pachymetry, and computer-assisted corneal topography preoperatively and postoperatively. The potential visual acuity was tested by contact-lens overrefraction or the Potential Acuity Meter if necessary (PAM, Mentor O & O Inc., Norwell, Massachusetts). Corneal haze was graded preoperatively and postoperatively as 0 (none), 0.5 (barely detectable), 1 (easily detectable, but not affecting refraction or retinoscopy), 2 (easily detectable and interfering with retinoscopy and refraction), and 3 (obscuring iris details).

The patients were then placed under the excimer laser, topical proparacaine hydrochloride was applied, and a circular protractor was placed on the globe at the corneoscleral limbus and oriented by using a landmark observed at the slit lamp preoperatively. A few pulses were then applied with the slit maximally narrowed to ensure proper orientation of the slit relative to the corneal cylinder and to acquaint the patient with the sensations associated with laser ablation. The corneal epithelium was then removed with a blunt spatula, after which the eye was fixed by using a vacuum fixation ring, and the area of treatment centered over the entrance pupil, while the patient fixated on a flashing centration light. The computer was programmed to perform cylindric ablations greater than or equal to 80% of the preoperative cylindric error, adjusted to the corneal plane. In one patient with postkeratoplasty astigmatism that measured 12 diopters, we programmed 50% correction and in two other patients a 66% correction was attempted. The desired refractive change was programmed into the computer in minus cylinder form (for example, plano -6.00×180 designed to induce 6 diopters of flattening in the vertical meridian). The blades are oriented by the computer to be parallel to the axis of refractive cylinder expressed in minus cylinder form, thereby flattening the cornea in the appropriate (steeper) meridian.

Patients were treated postoperatively with a combination tobramycin sulfate (0.3%)/dexamethasone sodium phosphate (0.1%) ointment and semipressure patching, and were examined daily or every other day until reepithelialization was complete. They were then treated with 1% prednisone acetate four times daily for two weeks, three times daily for four weeks, and twice daily for four more weeks. Two weeks and one, two, three, four, and six months postoperatively, refraction, keratometry, ultrasonic pachymetry, and computer-assisted topography were performed by the same masked observer. A paired two-tailed *t*-test was used to compare preoperative and postoperative measurements. Data were computed as mean ± standard deviation.

Results

Patients—We performed superficial toric ablations with the excimer laser on 12 patients who had disabling postkeratoplasty astigmatism that had persisted for more than one year after removal of all corneal sutures. All patients were contact-lens intolerant and were unable to tolerate the high cylindric prescription in their spectacles. Prekeratoplasty diagnoses were keratoconus (Patients 3 through 6, 8, 9, 11, and 12), herpes (Patient 1), Fuchs' dystrophy (Patient 7), corneal scar (Patient 10), and chemical burn (Patient 2). Preoperative measurements disclosed that all patients except one (Patient 2) had potential visual acuity of 20/20. Patient 2, with a history of posttraumatic endophthalmitis, had a preoperative potential visual acuity of 20/60 as determined by the Potential Acuity Meter. Preoperative and postoperative refrac-

TABLE 1
PATIENT DATA*

PATIENT NO., GENDER, AGE (YRS)	PREOPERATIVE REFRACTION (DIOPTERS)	PREOPERATIVE VISUAL ACUITY WITHOUT CORRECTION	PREOPERATIVE VISUAL ACUITY WITH CORRECTION	DESIRED CORRECTION	POSTOPERATIVE REFRACTION (DIOPTERS)	POSTOPERATIVE VISUAL ACUITY WITHOUT CORRECTION	POSTOPERATIVE VISUAL ACUITY WITH CORRECTION	TIME (MOS)
1, M, 76	+3.50 −12.00 × 5	3/200	20/40	Plano −6.00	Plano −8.00 × 178	20/400	20/25	9
2, M, 37	−0.75 −6.00 × 135	20/400	20/100	Plano −10.00	Plano −2.75 × 18	20/100	20/60	14
3, M, 72	−6.50 −2.25 × 42	20/400	20/30	−3.00 −2.25	−5.00 −2.75 × 25	20/400	20/30	7
4, F, 27	−3.00 −5.00 × 157	20/100	20/30	Plano −4.75	+2.50 −0.50 × 6	20/30	20/20	12
5, F, 52	−9.25 −4.00 × 55	20/400	20/30	−8.5 −3.75	−1.50 −6.00 × 33	20/400	20/20	7
6, M, 44	−4.00 −5.00 × 106	20/200	20/30	Plano −4.75	+1.50 −10.50 × 113	3/200	20/30	6
7, F, 83	−1.00 −6.00 × 170	20/300	20/30	−2.00 −4.00	−0.50 +1.00 × 180	20/25	20/20	6
8, M, 63	−5.00 −14.00 × 133	20/400	20/100	−6.00 −12.00	+12.50 −6.00 × 148	20/300	20/50	6
9, F, 29	−13.25 −6.25 × 55	10/400	20/20	−11.50 −4.00	+5.00 −2.50 × 64	10/200	20/20	6
10, F, 80	−6.50 −8.50 × 42	5/200	20/30	−2.75 −6.75	+0.50 −3.00 × 144	20/100	20/30	7
11, M, 46	−2.75 −3.75 × 29	10/200	20/25	−1.75 −3.75	+0.50 −3.50 × 111	20/80	20/20	6
12, M, 36	+2.50 −11.00 × 135	20/400	20/20	−10.00	+3.50 −6.00 × 136	20/100	20/25	7

*Corrected visual acuity represents visual acuity with spectacles.

tive error, visual acuity, and keratometric measurements were determined (Tables 1 and 2). The patients were followed up for a minimum of six months, and for a mean of eight months (range, six to 14 months).

Visual acuity—Uncorrected visual acuity improved by at least one Snellen line in nine of 12 patients (75%), decreased by one line in one patient, and did not change in two patients (Table 1). The visual acuity corrected with spectacles improved in seven patients by at least one line, decreased in one patient, and was unchanged in four patients. The visual acuity of Patient 6, whose uncorrected visual acuity (3/200) was improved markedly with spectacles (20/30), had even greater improvement (20/25) with a gas-permeable contact lens.

Refractive astigmatism—Photorefractive keratectomy was performed on the basis of the total measured refractive cylinder corrected for the corneal plane in most of the patients. The attempted correction was plotted against the achieved correction ($R^2 = 0.40$) (Fig. 1). Patient 1, who had 12 diopters of astigmatism preoperatively, had a target correction of 6 diopters of cylinder, and Patients 7 and 9 had corneal ablations calculated to correct 66% of the initial refractive cylinder. The mean changes in refractive cylinder were determined (Fig. 2). The mean preoperative refractive cylinder was 7.0 ± 3.6 diopters. One month postoperatively, a significant reduction in refractive cylinder was achieved (3.1 ± 0.7 diopters, P = .001). A slight regression in the effect was first noticed two months postoperatively, and the average correction at most recent follow-up was 38%. The difference in the axis of refractive cylinder preoperatively and at the last follow-up disclosed a shift in the axis that ranged from 1 to 173 degrees, with a mean shift of 58 ± 62 degrees. Four patients (Patients 1, 2, 4, and 10) had overcorrection of their astigmatism, with a shift in the cylinder axis of more than 100 degrees.

TABLE 2
KERATOMETRIC CYLINDER*

PATIENT NO.	PREOPERATIVE DIOPTER	PREOPERATIVE AXIS	POSTOPERATIVE DIOPTER	POSTOPERATIVE AXIS
1	17.38	95	13.75	87
2	5.50	53	1.88	109
3	3.12	3	3.60	110
4	4.37	75	3.17	78
5	6.50	150	6.50	142
6	7.63	16	6.25	19
7	4.38	82	1.87	108
8	12.37	41	10.50	43
9	6.36	174	2.50	154
10	8.37	175	4.00	38
11	5.38	115	0.60	108
12	8.75	45	8.70	58

*Mean (± standard deviation) preoperative keratometric cylinder, 7.5 ± 4.0; mean (± standard deviation) postoperative keratometric cylinder, 5.2 ± 3.9 (P < .001).

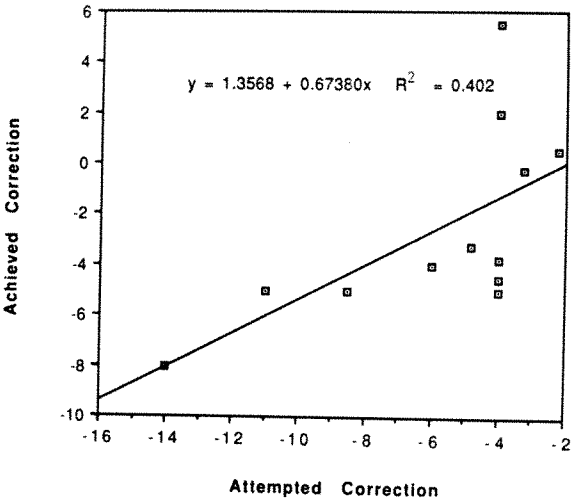


Fig. 1 (Campos and associates). Attempted correction vs achieved correction after photorefractive keratectomy for correction of postkeratoplasty astigmatism.

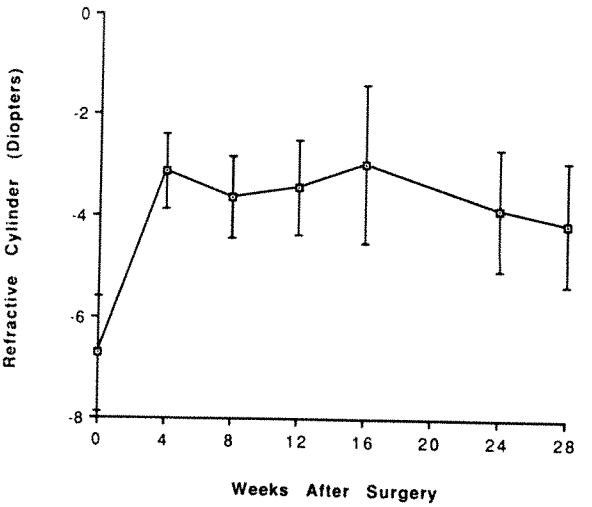


Fig. 2 (Campos and associates). Refractive cylinder (mean ± standard error) over time after photorefractive keratectomy for correction of postkeratoplasty astigmatism.

Excluding these four patients with overcorrected astigmatism, the change in refractive cylinder axis was 20.3 ± 25 degrees.

Keratometric astigmatism—The average preoperative keratometric corneal cylinder was 7.5 ± 3.9 diopters (Table 2). Considering the keratometric cylinder at the last follow-up of each patient, the average corneal cylinder was 5.2 ± 3.9 diopters (P = .001). Nine patients had a decrease in the corneal cylinder of at least 1.3 diopters, two patients did not have any change in keratometric cylinder, and the other patient showed an increase in corneal cylinder of 0.48 diopter, although the uncorrected visual acuity in this patient (Patient 3) did not change. The mean changes in the keratometric cylinder were determined (Fig. 3). The maximum decrease in the keratometric cylinder was noticed within three months postoperatively.

Spherical equivalent—The mean preoperative spherical equivalent was −7.4 ± 4.2 diopters. The mean changes in the spherical equivalent were determined (Fig. 4). Within the first eight weeks postoperatively, the mean spherical equivalent approached zero, and represented a

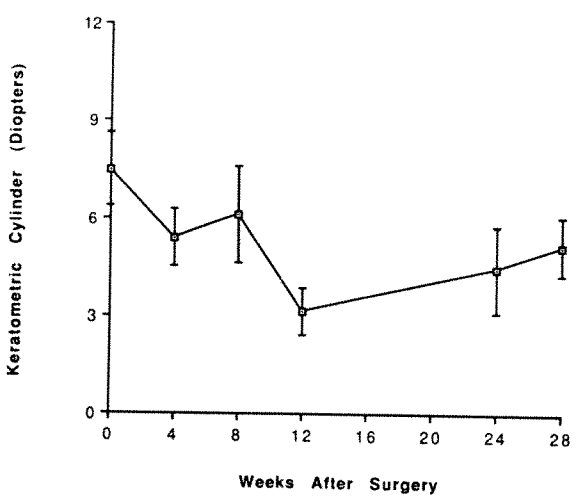


Fig. 3 (Campos and associates). Keratometric cylinder (mean ± standard error) over time after photorefractive keratectomy for correction of postkeratoplasty astigmatism.

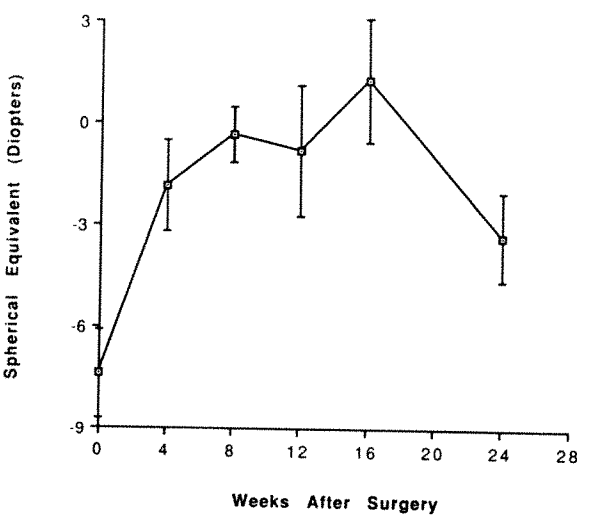


Fig. 4 (Campos and associates). Spherical equivalent (mean ± standard error) over time after photorefractive keratectomy for correction of postkeratoplasty astigmatism.

hyperopic shift that persisted until 16 weeks (Fig. 4). A slight decrease in the surgical effect on the spherical equivalent was noticed after four months in most of the patients. At the six-month follow-up, Patient 3 had a substantial regression of the surgical effect that had been present two months postoperatively (Fig. 5). Patient 4, with an intended cylindric correction of −4.75 diopters, had a reduction in myopia from −3.00 diopters preoperatively to −1.00 diopters postoperatively (Fig. 6). Patient 6, with an intended correction of 5.00 diopters of cylinder, developed a hyperopic shift in the spherical error; at the last follow-up, mean spherical equivalent was −3.3 ± 4.4 diopters ($P = .003$).

Pachymetry—The patients had a substantial decrease of the corneal thickness as an effect of excimer laser ablation. Two months postoperatively, the mean postoperative corneal thickness increased temporarily (Fig. 7). At the last follow-up, the average corneal thickness was 0.46 ± 0.05 mm ($P < .0001$), with an average reduction of 0.09 ± 0.05 mm.

Complications—In one patient (Patient 2), the epithelial defect had healed by 11 days postoperatively, whereas in all the other patients the defect healed within three days postoperatively. Patient 1 developed recurrent herpes simplex epithelial keratitis four weeks after keratoplasty (successfully treated with topical trifluridine). Another recurrence in this patient ten months after photorefractive keratectomy resulted in graft failure caused by apparent subsequent immunologic rejection. Despite frequent admonitions to report immediately any possible problems, this patient did not inform us in both instances of the decrease in vision and development of conjunctival injection for a week or longer after onset of symptoms, which delayed initiation of appropriate therapy. Other possible complications, such as corneal rejection, infection, or recurrent erosions, did not develop in our patients.

Corneal haze—The amount of corneal haze was graded by one of us (P.J.M.) for all patients. All of the corneas were graded as clear (0) preoperatively. The amount of haze postopera-

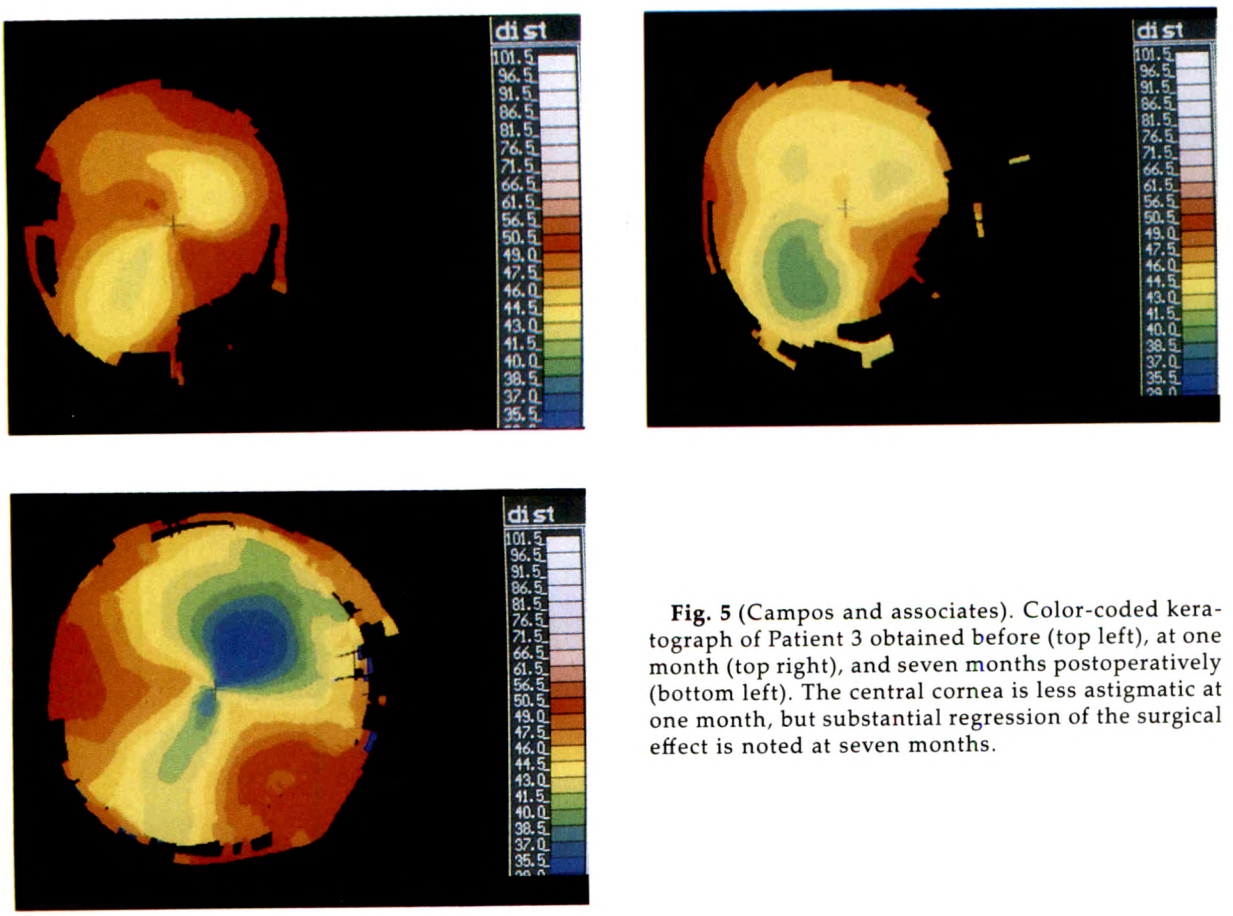


Fig. 5 (Campos and associates). Color-coded keratograph of Patient 3 obtained before (top left), at one month (top right), and seven months postoperatively (bottom left). The central cornea is less astigmatic at one month, but substantial regression of the surgical effect is noted at seven months.

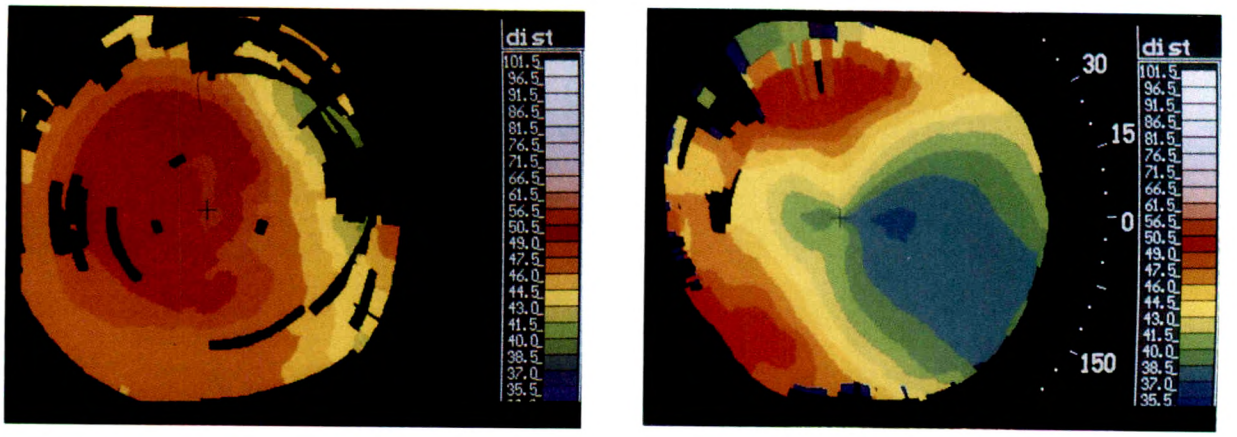


Fig. 6 (Campos and associates). Color-coded keratograph of Patient 4 obtained preoperatively (left) and eight months postoperatively (right). An overall flattening of the cornea was achieved, with apparent inferotemporal decentration of the zone of flattening.

tively ranged from 0.5 (barely detectable) to 1.0 (easily detectable, but apparently not interfering with retinoscopy or refraction).

Pain—The amount of pain experienced by these postkeratoplasty patients was generally mild and much less intense than that experienced by most patients we have treated with photorefractive keratectomy who have not had previous keratoplasty or other corneal surgical procedures.

Discussion

Although several techniques for correction of severe astigmatism after keratoplasty have been described, the refractive outcomes of these procedures, and particularly the predictability, are still unsatisfactory.[2-6,13-15] The limited surgical success is probably related to a poor understanding of the donor-host tissue relationship, which might be affected by such factors as faulty surgical technique (trephination and suture placement) and postoperative care. Attempts to correct postkeratoplasty astigmatism with relaxing incisions and compression sutures have yielded fairly unpredictable results.[16] Our results in this initial group of patients, after a single superficial ablation with the excimer laser, are not demonstrably superior to results of other small published surgical series in which incisions and compression sutures were used. Whether re-treating patients with undercorrected astigmatism will improve our overall results is unknown.

We wanted to evaluate the safety and efficacy of toric superficial corneal ablations for reducing postkeratoplasty astigmatism. Analysis of the corneal reepithelialization rate showed that the wound healing was not delayed in these postkeratoplasty patients when compared with the previously described reepithelialization rate in patients after photorefractive keratectomy for correction of myopia.[17,18] The delayed reepithelialization (11 days) in one patient may have been a consequence of the corneal alkali burn for which the keratoplasty was performed, and of mildly decreased tear production (confirmed by a preoperative Schirmer test). The

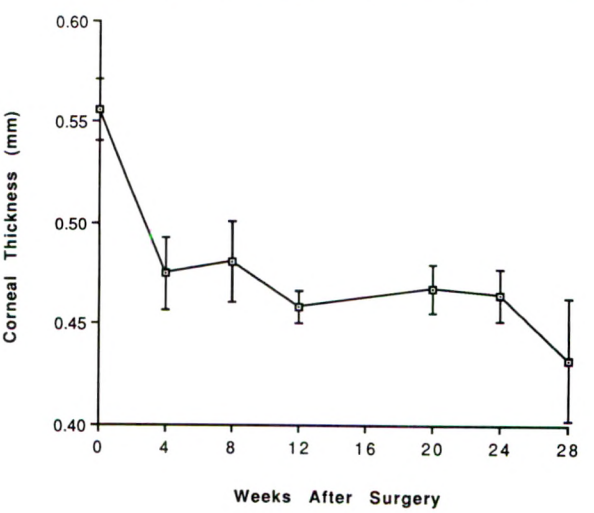


Fig. 7 (Campos and associates). Corneal thickness (mean ± standard error) as measured with ultrasonic pachymeter over time after photorefractive keratectomy for correction of postkeratoplasty astigmatism.

amount of corneal haze in these patients was minimal and appeared not to affect the final vision. The absence of intraoperative complications and of postoperative corneal infections or graft rejections, and relatively minor pain experienced by these patients, suggest that this is a fairly safe surgical procedure. Other surgical techniques for correction of postkeratoplasty astigmatism have been associated with various intraoperative and postoperative complications; relaxing incisions have resulted in corneal abscesses[19] and perforations,[20] and allograft reactions have complicated wedge resections (Table 3).[21]

Uncorrected visual acuity improved in nine patients, but only two patients had uncorrected visual acuity of better than 20/40. All of our patients had best-corrected visual acuities of better than 20/60, which is comparable to previous results.[10,11] Nine of the 12 patients had a reduction in refractive cylinder to a level that was tolerable with spectacles. Disparity between refractive and keratometric cylinder and changes in each were common; Patient 6, for example, had a reduction of 1.4 diopters on keratometric cylinder, but an increase in refractive cylinder of 5.5 diopters. Other investigators[22] have also demonstrated that refractive and keratometric cylinder may differ substantially in postkeratoplasty patients.

We observed a delayed loss of the initially achieved effect 12 weeks postoperatively (Fig. 5). It can be disappointing for patient and surgeon alike to observe an initially excellent optical result at one or two weeks postoperatively be lost as regression occurs. Other studies using the excimer laser for refractive surgical procedures have shown a regression of the initial effect also, usually within one to three months postoperatively.[17,18] We looked for a relationship between changes in corneal thickness over time and regression of refractive effect postoperatively, but no correlation could be demonstrated in our patients. Patients 6, 8, and 12, who had the most regression of refractive change, had a stable, unchanging corneal thickness postoperatively, even during and after the regression.

Other studies using the excimer laser for photorefractive keratectomy for myopia have indicated better results in patients whose preoperative myopia was less than 5.00 diopters.[17,18] In our study, we did not observe a similar correlation between preoperative cylindric error and the accuracy of the surgical outcome.

In five patients we noted a corneal flattening in excess of that predicted merely on the basis of flattening the steep meridian. The preoperative flat meridian, in which a uniform depth of ablation is created, was also flattened (Fig. 6). As we have noted before,[13] this extra effect will have to be considered when programming an astigmatic correction with the excimer laser.

Surgical management of disabling astigmatism after keratoplasty is currently unsatisfac-

TABLE 3
PREVIOUS STUDIES OF SURGICAL TREATMENT FOR POSTPENETRATING KERATOPLASTY ASTIGMATISM COMPARED WITH OUR STUDY

STUDY (IN ORDER OF PUBLICATION)	NO. OF CASES	SURGICAL TECHNIQUE	PROCEDURE USED TO PLAN SURGICAL TECHNIQUE	REDUCTION OF ASTIGMATISM (%)	KERATOMETRIC CYLINDER REDUCTION (DIOPTERS)	POSTOPERATIVE PERIOD (MOS)
Troutman and Swinger[9]	4	Arcuate keratotomy	Keratometry	75.0	8.40	4
Krachmer and Fenzl[16]	16	Arcuate keratotomy	Keratometry	42.5	4.25	8.2
Sugar and Kirk[13]	14	Arcuate keratotomy	Keratometry	60.0	7.50	Not available
Mandel, Shapiro, and Krachmer[21]	21	Arcuate keratotomy and compression sutures	Keratometry	67.0	6.56	6 to 9
McCartney and associates[19]	11	Relaxing incisions and compression sutures	Intraoperative keratoscopy	68.0	7.95	13.5
Cohen, Tripoli, and Noecker[14]	7	Arcuate keratotomy	Photokeratoscopy	69.8	6.52	7
Maguire and Bourne[15]	5	Arcuate keratotomy or relaxing incisions	Photokeratoscopy	37.7	3.00	Not available
Frangieh, Kwitko, and McDonnell[18]	7	Relaxing incisions and compression sutures	Computer-assisted corneal topography	81.1	8.20	12.3
Our study	12	Photorefractive keratectomy	Refraction	38.0	2.30	7.7

tory. On the basis of our results, the use of the excimer laser to perform toric ablations in patients with severe astigmatism after keratoplasty appeared to be safe, but the refractive results regressed substantially in some patients, typically at about or after three months. We have yet to re-treat any patients with undercorrected astigmatism, and thus cannot comment on whether a repeat surgical procedure would yield better results.

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Fungal Keratitis From Nylon Line Lawn Trimmers

Thomas E. Clinch, M.D., Matthew J. Robinson, M.D., Bruce A. Barron, M.D., Michael S. Insler, M.D., Keith Liang, M.D., and Herbert E. Kaufman, M.D.

Ocular trauma from nylon line lawn trimmers is becoming more prevalent. Previous case reports have described penetrating trauma caused by these tools. We managed three cases of fungal keratitis caused by injuries from nylon line trimmers. Fungal keratitis should be strongly considered as the cause of any corneal ulcer related to trauma from a nylon line lawn trimmer.

THE NYLON LINE LAWN TRIMMER is a commonly used garden tool. Because the trimmer lacks a blade, the tool is often perceived by the user to be safe. However, the nylon line lawn trimmer operates at high velocity (6,000 to 8,500 rpm) and fragments of the nylon cord are constantly broken off during the process. These nylon fragments and associated debris are propelled outward at high speeds, and can cause severe ocular injury.[1-4] On the basis of data from the National Electronic Injury Surveillance System, the United States Consumer Product Safety Commission estimated that there were 1,336 ocular injuries related to the use of power lawn trimmers or edgers in 1991.[5]

Previous case reports described penetrating trauma, including corneal laceration; cataract formation; intraocular foreign bodies; and bacterial, fungal, and multiorganism endophthalmitis.[1,3,4] Hyphema has also been found in a nonpenetrating ocular injury.[1,2] In a retrospective study, nylon line lawn trimmers were the fifth leading cause of penetrating ocular trauma.[1]

Nylon line lawn trimmer–related injuries may also cause serious ocular infection. Projectiles of dirt, vegetative matter, and debris (rocks, wires, and other materials), as well as nylon cord fragments, can transfer microorganisms to the eye. We managed three cases of fungal keratitis that resulted from the use of nylon line lawn trimmers.

Patients and Methods

Three patients with corneal ulcers resulting from injuries caused by nylon line lawn trimmers were referred to our institution over a three-month period. The following details were recorded for each case: age, gender, initial visual acuity, circumstances of the injury, extent of ocular injury, presence or absence of protective eyewear, medical and surgical treatment, culture results, and final visual acuity.

Case Reports

Case 1

In August 1991, a 54-year-old man developed foreign-body sensation in his left eye while he was using a nylon line lawn trimmer. Examination disclosed a corneal abrasion and antibiotic ointment and a patch were applied. The next day, a paracentral corneal ulcer was present. A culture was obtained and a treatment regimen of 0.3% tobramycin drops and ointment was initiated. Satellite lesions were observed three days later, and a corneal smear disclosed fungal hyphae. Hourly therapy with topical 0.1% amphotericin and 5% natamycin was begun. Clinical signs of improvement were observed with this regimen; however, one week later, the ulcer was noted to enlarge rapidly over a 24-hour period. Corneal cultures grew *Staphylococcus simulans* but were negative for fungus. Corneal smears again disclosed fungal elements. Intensive treatment with fortified antibiotics (1.36% gentamicin and 5% cefazolin every 30 minutes) and 1% prednisolone acetate twice daily was added to the medical regimen. Treatment with

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From the LSU Eye Center, Louisiana State University Medical Center School of Medicine, New Orleans, Louisiana.

Reprint requests to Herbert E. Kaufman, M.D., LSU Eye Center, 2020 Gravier St., Suite B, New Orleans, LA 70112-2334.

0.1% amphotericin every hour was continued. Two days later, the patient was referred to our institution.

On initial examination, visual acuity was counting fingers at three feet. A large corneal ulcer with satellite lesions was present (Fig. 1). Periodic acid-Schiff and calcofluor white staining of corneal specimens disclosed fungal hyphae. Corneal cultures were negative for bacteria and fungi. The patient was treated intensively with topical fortified antibiotics (5% cefazolin and 1.36% gentamicin every 30 minutes), as well as hourly 5% natamycin. The corneal ulcer resolved over the next several weeks. However, a dense central corneal scar remained. Penetrating keratoplasty was performed in October 1991, for visual rehabilitation. Five months postoperatively, the patient's best-corrected visual acuity was 20/40.

Case 2

In August 1991, a 32-year-old man felt a foreign object strike his left eye while he was using a nylon line lawn trimmer. He was subsequently examined by an ophthalmologist and treated with a regimen of topical ciprofloxacin every two hours for a corneal ulcer. After five days of treatment, the ulcer continued to enlarge and the patient was referred to our institution.

On initial examination, uncorrected visual acuity was 20/200. A 1.4 × 1.7-mm central corneal ulcer was present (Fig. 2). The anterior chamber showed moderate inflammation with no hypopyon. Corneal smears and cultures were obtained. Intensive treatment with topical fortified antibiotics (cefazolin, gentamicin, and neomycin) was begun. On the second hospital day, calcofluor white staining of a corneal smear disclosed septate hyphae. Topical 5% natamycin every 30 minutes was added to the treatment regimen. The corneal ulcer began to improve throughout the next week. Uncorrected visual acuity recovered to 20/40. Corneal cultures grew *Curvularia* organisms two weeks after admission. Treatment with the natamycin was tapered and the ulcer resolved. The patient did not return for subsequent examination, but a recent telephone interview disclosed that he was doing well.

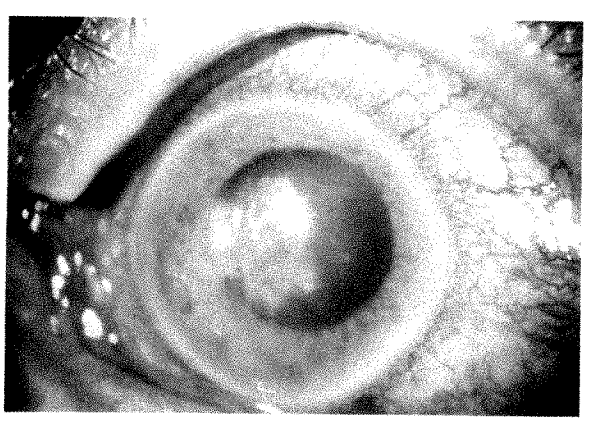


Fig. 1 (Clinch and associates). Case 1. Fungal corneal ulcer with satellite lesions.

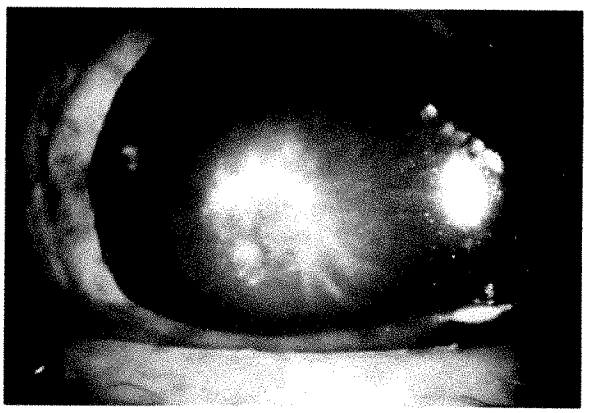


Fig. 2 (Clinch and associates). Case 2. Fungal corneal ulcer with a feathery edge to the infiltrate.

Case 3

In June 1991, a 14-year-old boy noted a foreign-body sensation in his right eye while he was using a nylon line lawn trimmer. The next day, examination by an emergency room physician disclosed a corneal abrasion. Tobramycin ointment was applied and the eye was patched. One day later, the patch was removed and a corneal ulcer was observed. The patient was referred to our institution.

On initial examination, uncorrected visual acuity was 20/50. A 2.6 × 2.2-mm corneal ulcer was present. The edges of the infiltrate had a feathery appearance. Corneal cultures and smears were obtained and an intensive treatment regimen of topical fortified antibiotics (cefazolin, gentamicin, and Neosporin) was initiated. Corneal smears and cultures were initially negative for organisms. Because of a high suspicion of a fungal origin, a corneal biopsy was performed on the third hospital day. The biopsy specimen was stained for fungi (Gomori methenamine silver and periodic acid-Schiff), but no organisms were seen. Cultures obtained at that time were also negative for organisms. The patient was subsequently discharged with

a treatment regimen of fortified cefazolin and gentamicin.

Two weeks after the injury, *Curvularia* organisms were detected in the inoculation streaks of the original fungal culture. The patient was treated with 5% natamycin. The clinical response was rapid. By August 1991, uncorrected visual acuity had returned to 20/20 and only mild paracentral corneal scarring remained.

Results

All of the patients claimed to have had 20/20 visual acuity before the injury. None of the patients was wearing protective eyewear at the time of injury. Two of the three patients did not seek medical attention until one day after the trauma. In two patients, fungal smears and cultures were not obtained when the corneal ulcer was first identified and treatment was initiated, which delayed diagnosis. Visual recovery was good in all patients; however, only one patient regained 20/20 visual acuity.

Discussion

Filamentous fungal keratitis is associated with trauma with vegetative matter. The organism enters the corneal stroma at the time of injury.[6,7] Although filamentous fungal infections are more prevalent in the southern United States, they are also often encountered in rural northern areas where work habits and outdoor activity increase exposure.[6]

The infectious process resulting from filamentous fungi usually manifests in 24 to 48 hours, but can occasionally be more indolent.[6] Because of the potential for devastating consequences from delayed diagnosis, we think all corneal abrasions caused by trauma from nylon line lawn trimmers should be closely followed up. We recommend initial treatment similar to that used for patients with corneal abrasions from contact-lens wear, that is, broad spectrum antibiotics without pressure-patching. Any nylon line lawn trimmer–related corneal ulcer should be viewed with a high index of suspicion for a fungal origin. Corneal smears and appropriate cultures should be obtained promptly. Most filamentous fungi grow in Sabouraud's medium within three days; however, as many as 25% of cultures may show no growth for as long as 14 days.[8,9] Cases 2 and 3 exemplify this delayed growth and demonstrate the need to obtain appropriate corneal smears when an ulcer is first detected. At our institution, periodic acid-Schiff, Giemsa, and calcofluor white stains are used. If initial cultures and smears are negative for organisms and the patient does not respond to therapy, cultures and smears should be repeated. Corneal biopsy is usually successful for the diagnosis of fungal keratitis, although occasionally, as in Case 3, a false-negative result occurs. Biopsy should be considered for any culture-negative progressive corneal ulcer caused by a nylon line lawn trimmer.

All of our patients responded to natamycin, which is the recommended initial treatment for corneal infections caused by filamentous fungus.[10,11] In two of our patients, *Curvularia* organisms, which are pigmented fungi, were isolated. Among filamentous fungi, the pigmented fungi (Dematiaceae) appear to have the highest success rate (90%) for treatment with natamycin.[12] We believe natamycin is the best antifungal drug for the initial treatment of keratomycosis caused by nylon line lawn trimmers. Debridement of the ulcer increases drug penetration and facilitates recovery.

These cases emphasize the need to closely follow up any patients with corneal trauma involving vegetative matter. None of these patients was wearing protective eyewear, which highlights the need for ophthalmologists to educate their patients about ocular protection.

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OPHTHALMIC MINIATURE

The informer turned and saw a cat sleeping on the second-floor sill. He lifted it and with stark, unsmiling malice, threw it down upon the face of the man beneath him. It landed all claws on Murphy and clung to his flesh until, in a brutal rage of agony, he threw it off.

Bristling and indignant, it fell on its feet, and a woman bent to it: 'That anyone could hurt a poor, harmless beast!" But as she touched it, it sped from her and left her snubbed.

After he had thrown it off there was a full moment's silence whilst he clung motionless before suddenly starting to scream as though someone had thrown vitriol into his eyes:

'I'm blinded.'

Then, as he opened his eyes and realized he spoke the truth, he caught his breath and sobbed stupidly: 'But I can't see.' His sob became a wail of horrified realization: 'I tell ye I can't see. I can't . . . I can't . . .'

Olivia Manning, *The Wind Changes*
New York, Penguin Books, 1937, p. 33

Topical Fibronectin in the Treatment of Keratoconjunctivitis Sicca

J. Daniel Nelson, M.D., Judy F. Gordon, D.V.M., and the Chiron Keratoconjunctivitis Sicca Study Group

Topical fibronectin was evaluated for the treatment of keratoconjunctivitis sicca in a multicenter, double-masked, controlled study in which 272 patients were randomly assigned to treatment. Patients with documented clinical evidence of keratoconjunctivitis sicca received either fibronectin, a vehicle alone, or a commercially available artificial tear. Evaluation at baseline, 21, 42, and 63 days consisted of patient self-evaluation of symptoms, rose bengal and fluorescein staining, tear breakup time, Schirmer's testing, and conjunctival impression cytology. Although all groups showed improvements in most study variables during the course of the study, there were no statistically significant differences found between any of the groups. Topical fibronectin does not appear to be more effective than artificial tears in the treatment of keratoconjunctivitis sicca.

THERAPY for keratoconjunctivitis sicca remains symptomatic, and includes artificial tear solutions, lubricating ointments, ocular inserts, and punctal occlusion. Topical application of artificial tear solutions remains the primary method of treatment. An ophthalmic solution containing a therapeutic agent effective in the treatment of dry eye would be desirable.

Fibronectin is an adhesive glycoprotein that is a component of the basement membrane. In addition to its activity as a binding agent that promotes cell-to-cell and cell-to-substrate adhesion, fibronectin also has a role in cell migration, wound healing, and cytoskeletal organization. Fibronectin has been shown to promote the attachment of rabbit corneal endothelial cells to plastic culture dishes.[1] The addition of fibronectin to cultures of transformed cells allows the cells to adhere to and move across the surface of the plastic culture plates.[2,3] In vitro studies have shown that endogenously produced fibronectin forms a matrix over the underlying stroma of corneas subjected to superficial keratectomy, thus allowing epithelial cell migration.[4-6] The in vivo induction of corneal lesions has also been shown to be accompanied by fibronectin deposition during the subsequent healing period.[7-10]

The presence of endogenous fibronectin on the surface of the injured cornea led to clinical application of exogenous fibronectin in patients with keratoconjunctivitis sicca. Kono and associates[11] used autologous fibronectin in treating a group of 12 patients with keratoconjunctivitis sicca associated with Sjögren's syndrome. Treatment with fibronectin resulted in a reduction in rose bengal and fluorescein staining as well as improvement in the subjective symptoms of dry eye.

On the basis of data that suggested a role of fibronectin in the healing of ocular surface disorders, including keratoconjunctivitis sicca, a multicenter double-masked, vehicle-controlled and placebo-controlled trial was conducted to study the safety and efficacy of fibronectin in the treatment of patients with keratoconjunctivitis sicca.

Material and Methods

Patients—Over a 16-month period (from April 1988 to August 1989), 272 patients with keratoconjunctivitis sicca were enrolled in this clinical trial. Patients eligible for enrollment

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From the Department of Ophthalmology, Ramsey Clinic, St. Paul-Ramsey Medical Center, St. Paul, Minnesota; and Department of Ophthalmology, University of Minnesota, Minneapolis, Minnesota (Dr. Nelson); and Chiron Ophthalmics, Irvine, California (Dr. Gordon and Chiron Keratoconjunctivitis Sicca Study Group). Dr. Gordon is an employee of Chiron Ophthalmics.

Reprint requests to J. Daniel Nelson, M.D., Department of Ophthalmology, St. Paul-Ramsey Medical Center, 640 Jackson St., St. Paul, MN 55101.

were required to meet at least one of the following entry criteria: (1) wetting of less than 5 mm in five minutes when Schirmer's testing is performed without topical anesthesia and a superficial punctate staining score of at least 2 (on a scale of 1 to 4); (2) wetting of less than 5 mm in five minutes when Schirmer's testing is performed without topical anesthesia and a rose bengal staining score greater than 3 (on a scale of 1 to 9); (3) rose bengal staining score greater than 3 (on a scale of 1 to 9) and a patient self-evaluation score of at least 50 on a visual analogue scale of 0 to 100 on three of nine dry-eye symptoms (pain, burning, itching, dryness, foreign-body sensation, tearing, blurring, photophobia, and other); and (4) superficial punctate staining score of at least 2 and a patient self-evaluation score of at least 50 on three dry-eye symptoms. In addition to meeting these diagnostic criteria, all patients were required to be of legal age and to have read and signed a written informed consent form.

Patients with dry eye associated with congenital alacrima, vitamin A deficiency, Stevens-Johnson syndrome, ocular pemphigoid, drug-induced pseudopemphigoid, ocular chemical burns, neurogenic hyposecretion, lagophthalmos, inadequate eyelid closure, trachoma, ocular surface irregularities, trichiasis, or ocular radiation injury were excluded from the study. Other exclusionary criteria were uncontrolled blepharitis; rosacea keratoconjunctivitis; corneal perforations; preexisting blindness, glaucoma, or uveitis; administration of medications known to cause ocular dryness; uncontrolled ophthalmic or systemic infections; serious immune deficiency or immunosuppressive therapy; pregnancy; and lactation. Patients with a history of viral hepatitis or infection with human immunodeficiency virus were also excluded.

Study design—The study was a double-masked, controlled parallel group trial in which patients were randomly assigned to treatment and was conducted at 33 clinical sites. The experimental protocol was reviewed and approved by the Institutional Review Board at each study center.

After determination of eligibility, all patients were required to complete 14 days of washout, during which they administered only an unpreserved lubricating agent (Refresh, Allergan Pharmaceuticals, Irvine, California). At the end of this 14-day period, patients were examined again to determine eligibility. The unpreserved lubricating agent was used to eliminate the effect of preservatives on the patient's clinical signs and symptoms. Patients who had an improvement in clinical signs and symptoms during the washout period, and who no longer satisfied the entry criteria, were not enrolled in the study.

Eligible patients were randomly assigned to one of three treatment groups: fibronectin ophthalmic solution (3.5 mg/ml); vehicle solution, consisting of all components of the fibronectin solution, without fibronectin; or a commercially available artificial tear product (Liquifilm Tears, Allergan Pharmaceuticals). The identity of the treatment was masked to investigators and patients.

On day 1 of the study, each patient administered one drop of the study medication (fibronectin, vehicle, or artificial tear) into each eye six to eight times daily. Treatment was continued for 42 days, after which patients returned to administration of only an unpreserved lubricating agent (Refresh) for three weeks (that is, through day 63). Separate computer-generated randomization codes were prepared for each clinical site, with treatment groups in blocks such that an equal number of patients at each center were treated with fibronectin, vehicle, and artificial tear. No other topical ophthalmic medication was allowed at any time during the study, and Refresh was provided to all study patients to ensure compliance. Systemic medications that were considered necessary for the patients' welfare, and that did not interfere with the study, were allowed. Patients who were self-administering oral beta blockers, diuretics, antidepressants, or estrogens were instructed to make no changes in their treatment regimen to avoid any possible effects on the level of ocular dryness.

Study medications—The fibronectin ophthalmic solution (3.5 mg/ml) consisted of lyophilized plasma fibronectin reconstituted in sterile saline solution that contained 0.5% chlorobutanol as a preservative. The lyophilized plasma fibronectin contained albumin and sucrose as stabilizers, and sodium chloride, sodium dihydrogen phosphate, and sodium hydrogen phosphate as buffering agents.

The vehicle solution consisted of the stabilizers and buffering agents found in fibronectin ophthalmic solution (that is, albumin, sucrose, sodium chloride, sodium dihydrogen phosphate, and sodium hydrogen phosphate). These materials were reconstituted in sterile saline

solution that contained 0.5% chlorobutanol as a preservative.

The artificial tear solution consisted of Liquifilm Tears, a commercially available artificial tear solution that contained polyvinyl alcohol 1.4%, sodium chloride, and chlorobutanol 0.5% in purified water.

Schedule of observations—Patients were examined 14 days before enrollment in the study, and then on day 1 to determine eligibility for the study. During the 42-day treatment period, patients were examined on day 21 (three weeks) and day 42 (six weeks). All patients were required to return for a follow-up visit on day 63 (nine weeks). Each patient visit included a complete ocular examination, which consisted of slit-lamp biomicroscopy, dilated fundus examination (day 1 and day 42), Schirmer's testing without anesthesia, and measurement of visual acuity, intraocular pressure, tear meniscus height, and tear breakup time.

The primary objective signs that were evaluated at each examination were fluorescein staining and rose bengal staining. Fluorescein staining was scored by the investigator on a scale of 0 to 4 (absent to severe staining) on the basis of comparison of the investigator's findings with a panel of standardized diagrams of staining provided on each data form. To evaluate fluorescein staining, five areas of the cornea (central cornea and then four equal peripheral areas) were individually scored, with a total maximum score of 20 per eye (40 for both eyes). Rose bengal staining was scored similarly, on a scale of 0 to 3 (absent to severe staining), with the degree of staining recorded separately for the temporal conjunctiva, cornea, and nasal conjunctiva. The total rose bengal staining score for each eye was 9, or 18 for both eyes. For both rose bengal and fluorescein staining in which only one eye was treated, the score was doubled to produce a comparable value for analysis.

A subset of the full study population also underwent serial conjunctival impression cytology, with samples obtained from the superior bulbar, temporal bulbar, nasal bulbar, and inferior palpebral conjunctiva to evaluate the degree of squamous metaplasia. Each region yielded a score ranging from 0.0 to 3.0 (normal cells to severe squamous metaplasia). Temporal and nasal specimens were considered a single specimen. The maximum impression cytology score was 18.0 for both eyes, with the score doubled for analysis when only one eye was treated. All impression cytology samples were evaluated in a masked fashion by a single reading center, according to previously described cytologic techniques for grading conjunctival squamous metaplasia.[12]

In addition to these clinical signs, a questionnaire was completed by the patients at each examination. Subjective symptoms were evaluated by each patient on a visual analogue scale of 0 to 100 (0 represents absent, 100 represents severe). Scores for nine symptoms (pain, burning/stinging, itching, dryness, foreign-body sensation, tearing, blurring of vision, light sensitivity, and other) were averaged to produce an overall symptom score. Additionally, patients rated their overall improvement on a visual analogue scale of 0 to 100 (no improvement to marked improvement).

Compliance levels were gauged through questions directed to the patient (whether the patient adhered to the treatment regimen all the time, most of the time, or not at all), as well as by measurement of the residual volume of solution in each dropper bottle returned by the patient.

Statistical analysis–Extensive statistical analyses were performed on the data generated in this study. The initial analysis was a direct comparison of the treatment groups at each time point in the study, conducted on the full study population. A comparison of the change from baseline for each treatment group was also performed for the full study population. Additional analyses were performed on numerous subgroups of the overall population (patients 60 years old and older, patients younger than 60 years, patients with Sjögren's syndrome–related keratoconjunctivitis sicca, patients with arthritis, patients with age-related keratoconjunctivitis sicca, a subgroup of patients who were severely affected, and a subgroup of patients whose keratoconjunctivitis sicca was determined on the basis of impression cytology findings). Results of the subgroup analyses were not significantly different when compared to the results of the overall population analysis.

Mean values were determined with standard deviations. Continuous variables and ordered categorical variables were analyzed by using individual *t*-test comparisons of group means at each visit. Differences between groups in change from baseline were analyzed by using the chi-square test. For some analyses, continuous variables were converted to categorical var-

TABLE 1
PATIENT DEMOGRAPHICS AND DISPOSITION

TREATMENT	MEAN AGE (YRS) (± STANDARD DEVIATION)	NO. OF PATIENTS				
		FEMALES	ENTERED	COMPLETED	DISCONTINUED	TERMINATED
Fibronectin	60 ± 14	94	103	80	11	12
Vehicle	61 ± 14	59	69	55	6	8
Control	69 ± 14	82	95	86	7	2
Total	63 ± 15	235	267	221	24	22

iables and analyzed by using the chi-square test.

Results

Patient population—We enrolled 267 patients in this study. Of these 267 patients, 221 patients completed the study. Demographic characteristics and disposition of patients were analyzed (Table 1). For the most part, all treatment groups were comparable at baseline, although there was a disproportionate number of females enrolled in the study, as compared to males (235 vs 32).

Clinical signs—Both fluorescein and rose bengal staining improved in all groups during the course of the study (Tables 2 and 3). There were, however, no statistically significant differences between any of the groups. Tear break-up times and Schirmer's test scores did not change significantly during the study period.

At baseline, mean impression cytology scores were similar for all treatment groups (Table 4). These scores remained virtually unchanged for the duration of the study, with no significant differences seen between treatment groups at any of the time points. Similarly, the change from baseline was not substantial for any group.

Total mean symptom scores were similar for the four treatment groups at baseline (Table 5). All groups had a decrease in total symptom scores during the study. There were, however, no statistically significant differences between any of the groups.

Data on patient compliance suggested that most patients in the study complied with the treatment regimen all of the time. The mean volume of investigational material used per day between the three groups ranged from 0.82 to 0.93 g/day.

Most of the reported adverse reactions could be categorized as ocular irritation that included pain, burning, stinging, itching, redness, irritation, and foreign-body sensation. More fibronectin-treated and vehicle-treated patients terminated from the study because of adverse reactions than patients in the artificial tear group.

Discussion

The results of this double-masked, placebo-controlled, multicenter study in which patients were randomly assigned to treatment demonstrate that fibronectin had no greater therapeutic efficacy in patients with keratoconjunctivitis sicca than did the vehicle solution or Liquifilm

TABLE 2
MEAN SUPERFICIAL PUNCTATE STAINING SCORES*

DAY	FIBRONECTIN			VEHICLE			PLACEBO		
	NO. OF PATIENTS	MEAN	STANDARD DEVIATION	NO. OF PATIENTS	MEAN	STANDARD DEVIATION	NO. OF PATIENTS	MEAN	STANDARD DEVIATION
1	103	11.7	8.6	69	10.4	8.3	94	12.7	8.3
21	91	8.4	7.8	61	7.8	7.0	90	9.1	7.7
42	83	7.9	7.8	58	6.6	5.8	88	8.1	7.6
63	79	6.4	6.8	56	6.4	6.5	86	8.0	7.9

*Maximum superficial punctate staining score for each eye was 20 (40 for both eyes).

TABLE 3
MEAN ROSE BENGAL STAINING SCORES*

	FIBRONECTIN			VEHICLE			PLACEBO		
DAY	NO. OF PATIENTS	MEAN	STANDARD DEVIATION	NO. OF PATIENTS	MEAN	STANDARD DEVIATION	NO. OF PATIENTS	MEAN	STANDARD DEVIATION
1	103	8.5	4.0	69	8.8	4.2	95	9.1	4.2
21	91	6.8	4.9	61	6.6	4.7	90	6.5	4.1
42	83	6.2	4.6	58	6.0	4.5	88	5.6	4.5
63	79	5.5	4.1	56	5.9	4.2	86	6.3	4.4

*Maximum rose bengal staining score for each eye was 9 (18 for both eyes).

tears, a commercially available artificial tear solution. The total patient population (all treatment groups) had marked improvements from baseline with regard to the major clinical variables associated with keratoconjunctivitis sicca, that is, superficial punctate staining, rose bengal staining, and symptoms. However, these effects were no greater in the fibronectin-treated patients than in the control patients. The extensive analyses performed on the data generated in this trial did result in scattered statistically significant effects, but there was no pattern of findings that could suggest superior efficacy of any of the treatments tested. Adverse reactions were more frequent in the fibronectin-treated and vehicle-treated groups. These consisted of foreign-body sensation and burning, which suggested that the fibronectin and vehicle preparations may have been more irritating than the control preparations.

Fibronectin was proposed as a potential therapeutic agent for keratoconjunctivitis sicca on the basis of experimental evidence that supports the involvement of this glycoprotein in corneal wound healing. The presence of a matrix of endogenous fibronectin forming over corneas after superficial keratectomy[4-6] and the temporal relationship between fibronectin deposition, cellular migration, and corneal healing[9] suggest a role for fibronectin in ocular surface disease associated with a compromised corneal epithelium, such as severe keratoconjunctivitis sicca.

The data generated in this study suggest that the corneal substratum in patients with keratoconjunctivitis sicca, even those with a compromised corneal epithelium as evidenced by staining with fluorescein and rose bengal, differs substantially from the corneal stroma after superficial keratectomy or other types of injury. Although patients with keratoconjunctivitis sicca may have intense staining of the cornea or conjunctiva, or both, at initial examination, these areas of missing cells apparently heal rapidly with appropriate lubrication. This is in contrast to other cases in which the corneal epithelium has been damaged, and is resistant to healing. In more serious types of corneal damage, the loss of epithelium is accompanied by increased proteolytic activity, resulting in degradation of fibronectin from the anterior stroma and destruction of basement membrane. In such cases, treatment with exogenous fibronectin may be effective in promoting generation and adhesion of new epithelium. In the keratoconjunctivitis sicca syndrome, the loss of epithelial cells may not be followed by further degradation of the underlying tissue. If endogenous production of fibronectin is normal in these patients, and loss of epithelium is related

TABLE 4
MEAN CONJUNCTIVAL IMPRESSION CYTOLOGY SCORES*

	FIBRONECTIN			VEHICLE			PLACEBO		
DAY	NO. OF PATIENTS	MEAN	STANDARD DEVIATION	NO. OF PATIENTS	MEAN	STANDARD DEVIATION	NO. OF PATIENTS	MEAN	STANDARD DEVIATION
1	33	7.6	3.6	21	7.9	2.6	29	7.5	3.6
42	23	7.9	3.2	16	8.0	3.6	24	7.0	3.4
63	29	7.7	2.8	17	7.4	3.5	24	7.4	3.3

*Maximum impression cytology score was 9 (18 for both eyes).

TABLE 5
MEAN OVERALL SYMPTOM SCORES*

	FIBRONECTIN			VEHICLE			PLACEBO		
DAY	NO. OF PATIENTS	MEAN	STANDARD DEVIATION	NO. OF PATIENTS	MEAN	STANDARD DEVIATION	NO. OF PATIENTS	MEAN	STANDARD DEVIATION
1	101	307.0	151.1	68	320.1	154.6	92	305.2	152.3
21	87	247.6	163.9	61	235.7	148.1	89	214.6	138.8
42	82	223.7	127.0	54	220.2	138.7	88	213.7	150.9
63	78	225.3	142.7	56	241.2	150.0	82	216.5	159.7

*Nine subjective symptoms were scored by each patient on a scale of 0 to 100 (0 represents absent and 100 represents severe), which were then averaged to produce an overall symptom score.

primarily to the combined physical factors of aqueous deficiency and eyelid movement, addition of exogenous fibronectin would not be expected to be more efficacious than appropriate and frequent tear replacement with an artificial tear formulation.

Even though patient symptoms and clinical findings improved over the course of the study, the ocular surface did not improve as assessed by conjunctival impression cytology. This has previously been observed.[13] The reason for this is not known. There may be a primary ocular surface disorder in patients with keratoconjunctivitis sicca that does not respond to topical lubrication or may require certain, as yet unknown, substances to reverse squamous metaplasia. Reversal of squamous metaplasia in keratoconjunctivitis sicca may take longer than six weeks.[14]

Although the full study population, including the artificial tear control group, had significant improvements from baseline in rose bengal and fluorescein staining, as well as in symptoms, the artificial tear solution used as the placebo control is not necessarily more efficacious in the treatment of keratoconjunctivitis sicca than the products used by the patients before enrollment. In fact, Liquifilm tears was one of the multitude of commercial dry-eye products used by patients before the study in attempting to alleviate their condition. These findings suggest that participation in a clinical trial, with the frequent examinations and increased level of attention given to the patients, results in a high level of compliance with the treatment regimen, and a more positive response to a previously used artificial tear.

THE CHIRON KERATOCONJUNCTIVITIS SICCA STUDY GROUP

The participants in the Chiron Keratoconjunctivitis Sicca Study Group are as follows:

Principal Investigators: Penny A. Asbell, M.D., New York, New York; Alvan Balent, M.D., Fort Lauderdale, Florida; Richard Bowe, M.D., Tacoma, Washington; Terry Burris, M.D., Portland, Oregon; Delmar Caldwell, M.D., New Orleans, Louisiana; Dwight H. Cavanagh, M.D., Dallas, Texas; Donald J. Cinotti, M.D., Jersey City, New Jersey; Stuart Cole, M.D., Long Beach, California; William Constad, M.D., Jersey City, New Jersey; Richard M. Davis, M.D., Columbia, South Carolina; Deborah Di Stefano, M.D., Chattanooga, Tennessee; Peter C. Donshik, M.D., West Hartford, Connecticut; Steven Dunn, M.D., Southfield, Michigan; Randy Epstein, M.D., Chicago, Illinois; R. Linsey Farris, M.D., New York, New York; S. Lance Forstot, M.D., Littleton, Colorado; Gary Foulks, M.D., Durham, North Carolina; Bradley Fouraker, M.D., St. Louis, Missouri; M. H. Friedlaender, M.D., La Jolla, California; David Heidemann, M.D., Southfield, Michigan; Richard Keates, M.D., Irvine, California; Richard Lembach, M.D., Columbus, Ohio; Michael A. Lemp, M.D., Washington, D.C.; Lawrence Lohman, M.D., Kent, Ohio; Daniel Long, M.D., Gretna, Louisiana; Osvaldo Lopez, M.D., Chicago, Illinois; William Mathers, M.D., Washington, D.C.; James P. McCulley, M.D., Dallas, Texas; Robert McCulloch, M.D., Phoenix, Arizona; Alan Mindlin, M.D., Pontiac, Michigan; Richard Norden, M.D., Ridgewood, New Jersey; Stephen Pascucci, M.D., Scranton, Pennsylvania; Henry Perry, M.D., Rockville Centre, New York; Francis Price, M.D., Indianapolis, Indiana; Peter A. Rapoza, M.D., Madison, Wisconsin; J. James Rowsey, M.D., Oklahoma City, Oklahoma; H. Kaz Soong, M.D., Ann Arbor, Michigan; Michael Tapert, M.D, Mt. Pleasant, South Carolina; Michael Wagoner, M.D., Boston, Massa-

chusetts; and William Whitson, M.D., Indianapolis, Indiana.

Chiron Staff: Efraim Duzman, M.D., Medical Monitor; Judy Gordon, D.V.M., Director, Clinical Research; and Patti Lee, Senior Clinical Research Associate.

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Progression of Nonproliferative Diabetic Retinopathy and Visual Outcome After Extracapsular Cataract Extraction and Intraocular Lens Implantation

Glenn J. Jaffe, M.D., Thomas C. Burton, M.D., Evelyn Kuhn, Ph.D., Ardra Prescott, M.S., and Arthur Hartz, M.D.

Twenty-one patients with symmetric nonproliferative retinopathy who underwent extracapsular cataract extraction and intraocular lens implantation were followed up postoperatively for an average (± standard deviation) of 18 ± 7 months to determine the incidence of progression of diabetic retinopathy, the final visual acuity, and factors predictive of progression of retinopathy and final visual acuity. Progression of retinopathy, defined as the development of clinically significant macular edema, an increase in intraretinal hemorrhages or hard exudate, or the development of proliferative diabetic retinopathy, was assessed in both eyes of 19 patients; in two remaining patients, dense preoperative cataract in the fellow eye precluded comparison of retinopathy progression in the operated-on eye to progression in the fellow eye. Overall, retinopathy progressed in 14 of 19 operated-on eyes (74%). Cataract extraction was highly associated with asymmetric progression of nonproliferative retinopathy; it progressed only in the operated-on eye in seven of 19 patients (37%), but in no patients did progression occur in the fellow eye alone (P = .0078). Women had a significantly increased risk of progression of retinopathy in the operated-on eye compared to men (P = .005). Visual acuity improved in 19 of 21 operated-on eyes (86%); however, only 11 eyes (52%) achieved a visual acuity of 20/50 or better and only six eyes (14%) achieved a visual acuity of 20/25 or better. In only five eyes was the final visual acuity in the operated-on eye more than two lines better than the final visual acuity in the fellow eye. The visual acuity measured preoperatively by the Potential Acuity Meter was highly correlated with the final visual acuity (P = .0046). Patients treated with oral hypoglycemic agents had a worse visual prognosis than those treated with insulin (P = .035). Overweight women also had a significantly worse visual outcome than those patients with normal body weight (P = .021). The results of this study have important implications for the preoperative and postoperative management of diabetic patients undergoing extracapsular cataract extraction and intraocular lens implantation.

THE VISUAL PROGNOSIS for patients with preexisting diabetic retinopathy who undergo extracapsular cataract extraction and posterior chamber lens implantation is less favorable than for patients without retinopathy.[1-3] Reasons for decreased vision include neovascular glaucoma,[4] vitreous hemorrhage associated with proliferative diabetic retinopathy,[4] preexisting macular edema,[1] or postoperative macular edema.[5-7] In certain cases, nonproliferative diabetic retinopathy progresses only in the operated-on eye, suggesting that cataract extraction accelerates the course of the disease.[2,6-8]

Many questions remain regarding cataract extraction in diabetic patients with nonproliferative retinopathy. The incidence of asymmetric progression of diabetic retinopathy after cataract extraction is unknown, because all studies of asymmetric retinopathy progression have been retrospective. To determine the true incidence of this phenomenon, prospective data are needed. Factors predisposing to retinopathy progression and to poor visual outcome, such as age, gender, duration of diabetes,

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From the Department of Ophthalmology, Duke University, Durham, North Carolina (Dr. Jaffe); and Department of Ophthalmology (Drs. Burton and Hartz and Ms. Prescott) and Division of Biostatistics/Clinical Epidemiology (Drs. Kuhn and Hartz), Medical College of Wisconsin, Milwaukee, Wisconsin.

Reprint requests to Glenn J. Jaffe, M.D., Box 3802, Duke University Eye Center, Durham, NC 27710.

degree of diabetic control, and other systemic factors, have not yet been clearly defined. Furthermore, the role of an intact posterior capsule in the prevention of retinopathy progression and the role of laser photocoagulation in the visual prognosis remain to be determined. To begin to answer some of these questions, we determined the incidence of and risk factors for progression of nonproliferative diabetic retinopathy among patients who undergo extracapsular cataract extraction and intraocular lens implantation. A secondary goal was to determine the final visual acuity and risk factors for poor visual outcome in this patient population.

Patients and Methods

Patients were initially screened at the Medical College of Wisconsin to determine eligibility for the study. Patients were deemed eligible if they had preexisting symmetric nonproliferative diabetic retinopathy and did not have evidence of rubeosis, neovascular glaucoma, or proliferative diabetic retinopathy. From Sept. 9, 1987, through Jan. 10, 1991, we identified and followed up 24 patients who fulfilled the entry criteria. One of these patients was entered into the study but cataract extraction was subsequently cancelled, while another patient did not show up for all postoperative follow-up examinations. One other patient had a dense cataract that precluded adequate preoperative retinal examination; within one week postoperatively, he was found to have proliferative retinopathy that was presumed to have been preoperative in the operated-on eye. These three patients were excluded from the study; thus, 21 patients were entered. Each patient underwent a preoperative examination that included a detailed medical and ophthalmic history. All patients were examined 12 to 25 weeks after cataract extraction. Additional follow-up examinations were performed as indicated clinically. Ocular examinations were performed by one of us (T.C.B.) and included measurement of best-corrected Snellen visual acuity, slit-lamp biomicroscopy, measurement of intraocular pressure by applanation tonometry, and direct and indirect ophthalmoscopy with fundus contact-lens examination. Color photographs and fluorescein angiograms were obtained preoperatively and at 12 to 25 weeks postoperatively in all patients. Thereafter, color photographs and fluorescein angiograms were obtained as clinically indicated. In one patient, postoperative fluorescein angiography was not performed because of an allergic reaction that developed at the time of baseline angiography. At the initial preoperative examination, blood pressure, height, weight, and HbA_{1C} were measured in all patients. In 18 eyes, visual acuity was measured preoperatively with the Potential Acuity Meter (Mentor O & O, Inc., Norwell, Massachusetts). In two eyes, measurements with the Potential Acuity Meter were not possible because of dense cataract, and in a third patient, measurements were not possible because the patient could not respond satisfactorily to the testing procedure.

All data were recorded in a uniform manner on a standardized reporting sheet. For statistical analysis, the Snellen visual acuity was converted to the LogMAR scale as previously described.[9] The final visual acuity was determined at the last follow-up examination. Accelerated retinopathy was defined as the development of any of the following within six months postoperatively: new clinically significant macular edema, recurrent clinically significant macular edema in eyes that had preoperative resolution of macular edema after focal laser treatment, increased hard exudates or intraretinal hemorrhages in eyes with clinically significant macular edema at the baseline examination, or new-onset proliferative diabetic retinopathy. Clinically significant macular edema was defined according to Early Treatment of Diabetic Retinopathy Study criteria.[10] Using these definitions, we performed the following analyses. The risk of accelerated retinopathy in the operated-on eye was compared to the risk of accelerated retinopathy in the nonoperated-on eye. The final visual acuity in the operated-on eye was compared to preoperative visual acuity in the operated-on and nonoperated-on eyes, and to the final visual acuity in the nonoperated-on eye. The preoperative visual acuity determined by Potential Acuity Meter was compared to the final postoperative visual acuity. The following independent variables were tested for their association with an increased risk of accelerated retinopathy, or an association with the final visual acuity in the operated-on eye: age, gender, duration of diabetes, treatment with insulin or an oral hypoglycemic; histories of smoking, hypertension, renal disease, or cardiovascular disease (including stroke, transient ischemic attack, coronary artery disease, myocardial infarction, and congestive heart

failure); body mass index (weight/height^2), blood pressure, HbA_{1C}, visual acuity by Potential Acuity Meter, rubeosis, clinically significant macular edema; and preoperative or postoperative laser treatment.

As appropriate, the chi-square test for contingency tables unadjusted for continuity, the Spearman rank correlation, the Mann-Whitney U test, or the MacNemar test for matched paired data were used to determine the association between each variable and final visual acuity or accelerated retinopathy. For determination of the association of a given variable and final visual acuity, a difference of greater than 0.2 LogMAR unit (two lines on the Snellen chart) was considered significant. To test the association of final visual acuity and accelerated retinopathy with a given variable after adjusting for other variables, we used multivariate logistic analysis.

Results

Patient characteristics—Twenty-one patients were studied. The average age (± standard deviation) was 67.5 ± 9.0 years for all patients, was 69.5 ± 8.7 years for women, and was 64.1 ± 9.0 years for men. Thirteen patients (62%) were women. The average duration of diabetes (± standard deviation) was 21 ± 12.4 years. Fourteen patients (67%) were insulin-dependent, and seven (33%) were being treated with an oral hypoglycemic agent. Five patients (24%) were smokers, eight (38%) had a history of cardiovascular disease, and one (5%) had renal disease. At the initial examination, four patients (19%) were hypertensive (diastolic blood pressure greater than 90 mm Hg) and 13 patients (62%) were overweight (above ideal body weight). The mean HbA_{1C} (± standard deviation) was 11.5% ± 2.6%. The average preoperative visual acuity in the operated-on eye by LogMAR was 1.0 and ranged from 0.4 to 2.5 (mean Snellen visual acuity, 20/200; range, 20/50 to light perception). The mean visual acuity in the fellow eye by LogMAR was 0.39 and ranged from 0.1 to 1.5 (mean Snellen visual acuity, 20/50; range, 20/25 to 6/200). Preoperatively, six eyes had focal laser photocoagulation for clinically significant macular edema. In five of these eyes, clinically significant macular edema resolved before cataract extraction. In the sixth patient, clinically significant macular edema persisted despite treatment, and was present at the time of cataract extraction. In two eyes, the cataract was sufficiently opaque to preclude preoperative assessment of clinically significant macular edema. In these two eyes, baseline color fundus photography and fluorescein angiography were performed within one week of cataract extraction.

Postoperative course—All 21 patients underwent uncomplicated extracapsular cataract extraction. A posterior chamber intraocular lens was placed in 20 patients and an anterior chamber intraocular lens was implanted in one patient. No patient had vitreous loss or capsular rupture during the procedure. Thirteen of 21 operated-on eyes (62%) were treated with focal laser photocoagulation postoperatively for clinically significant macular edema. Of these 13 eyes, four were also treated with panretinal laser photocoagulation for concurrent proliferative diabetic retinopathy. Four eyes were eligible for focal laser treatment, but treatment was not administered because the patient either refused or did not show up for the laser appointment. Two patients underwent cataract extraction in the fellow eye during the follow-up period (six months and eight months after cataract extraction in the first eye, respectively). For these two patients, progression of retinopathy and final visual acuity were measured in the first eye operated on at the time cataract extraction was performed in the fellow eye. In 20 patients, the mean follow-up period (± standard deviation) was 18 ± 7 months (range, nine to 30 months). One patient died after the three-month follow-up examination.

Progression of diabetic retinopathy—In two patients, cataract was sufficiently dense in the fellow eye to preclude adequate assessment of progression of retinopathy; therefore, data were evaluated from the remaining 19 patients to assess progression of retinopathy in the operated-on eye compared to the fellow eye. Accelerated retinopathy developed in 14 of 19 operated-on eyes (74%) during the study period. Of these 14 eyes, new clinically significant macular edema developed in six eyes and recurrent clinically significant macular edema developed in five eyes. Of the remaining three eyes, accelerated retinopathy was characterized by increased intraretinal hemorrhages and hard exudates in two eyes and increased intraretinal hemorrhages in one eye, superimposed on clinically significant macular edema that was present at the baseline examination. Four eyes developed proliferative diabetic retinopathy in addition to clinically significant macular edema

or increased intraretinal hemorrhages or hard exudates. In three of these eyes, proliferative retinopathy developed 15 to 22 months after cataract extraction, and in a fourth eye, it developed two to four months postoperatively. None of the operated-on eyes developed neovascular glaucoma. Progression of retinopathy was highly asymmetric. The overall incidence of acceleration of retinopathy in the operated-on eye only was 37% (seven of 19 eyes). None of the patients had acceleration of retinopathy in the fellow eye only during the study period. The difference in accelerated retinopathy in the operated-on eye only compared to the fellow eye was highly statistically significant (P = .0078). Progressive diabetic retinopathy developed in both the operated-on and fellow eyes in seven patients (37%). In the fellow eye, accelerated retinopathy was characterized by the development of new clinically significant macular edema alone in five eyes, clinically significant macular edema and proliferative diabetic retinopathy in one eye, and proliferative diabetic retinopathy alone in one eye. Neovascular glaucoma developed in one fellow eye that had also developed accelerated retinopathy.

Five of 19 patients (26%) did not develop accelerated retinopathy in either eye during the study period. Among these patients, three developed transient cystoid macular edema in the operated-on eye by fluorescein angiography, within six months of cataract extraction. Two of these five patients had minimal preoperative nonproliferative diabetic retinopathy (less than ten microaneurysms, no intraretinal hemorrhages or hard exudates) and two had 20 to 25 microaneurysms with mild intraretinal dot hemorrhages and no hard exudates. The two patients with less than ten microaneurysms and the two patients with 20 to 25 microaneurysms had the least amount of preoperative retinopathy of all of the 19 patients studied.

Visual acuity—In 18 of 21 operated-on eyes (86%), the final visual acuity was better than the preoperative visual acuity. However, the final visual acuity was 0.4 or less by LogMAR (20/50 by Snellen) in only 11 eyes (52%) and 0.1 or less by LogMAR (20/25 by Snellen) in only six eyes (28%) (Fig. 1). For eyes with a final visual acuity worse than 20/25, visual acuity was limited by macular edema alone in eight eyes, macular edema and posterior capsular opacity in one eye, macular edema and keratoconus in one eye, macular fibrosis and posterior capsular opacity in one eye, macular pigment in one eye, and corneal opacity in one eye. In five

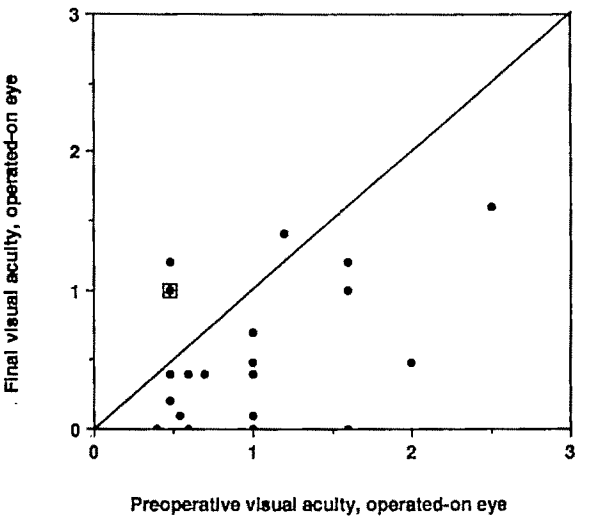


Fig. 1 (Jaffe and associates). Preoperative visual acuity in operated-on eyes compared to corresponding final postoperative visual acuity in operated-on eyes. Visual acuity recorded in LogMAR units. Point enclosed by rectangle corresponds to two eyes.

eyes, the reason for decreased vision was not apparent. Four eyes underwent YAG capsulotomies for posterior capsular opacification. Among these eyes, the final visual acuity ranged from 0.0 to 1.00 by LogMAR (20/20 to 20/100 by Snellen). Among fellow eyes, final visual acuity remained unchanged in seven eyes (33%), worsened in nine eyes (43%), and improved in five eyes (24%) (Fig. 2). Of the fellow eyes with an improvement in visual acuity, one eye had a spontaneous improvement of two lines on the Snellen chart without treatment, one eye was treated with focal laser photocoagulation for clinically significant macular edema, and extracapsular cataract extraction and posterior chamber intraocular lens implantation were performed on two eyes during the follow-up period. The average final visual acuity in the operated-on eye (± standard deviation), 0.55 ± 0.50, was almost identical to the average final visual acuity in the fellow eye (0.56 ± 0.57). In only five eyes was the final visual acuity in the operated-on eye more than two lines better than in the fellow eye; in seven eyes it was more than two lines worse (Fig. 3).

Association between preoperative and postoperative variables and asymmetric retinopathy progression or final visual acuity—We were unable to establish a correlation between any of the variables and asymmetric progression of retinopathy (increased retinopathy in the operated-on eye but not in the fellow eye) by univari-

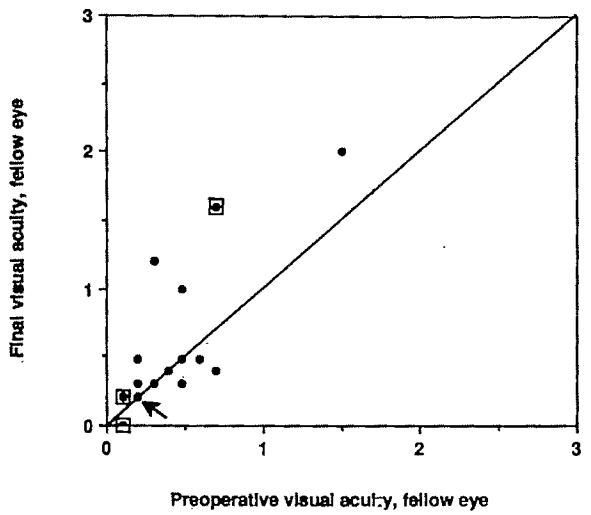


Fig. 2 (Jaffe and associates). Preoperative visual acuity in fellow eyes compared to corresponding final postoperative visual acuity in fellow eyes. Visual acuity recorded in LogMAR units. Points enclosed by rectangles correspond to two eyes. Point indicated by arrow corresponds to four eyes.

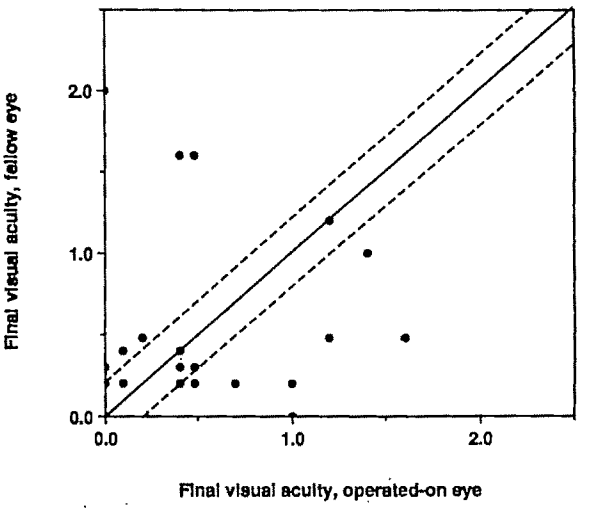


Fig. 3 (Jaffe and associates). Final postoperative visual acuity in operated-on eyes compared to final visual acuity in fellow eyes. Visual acuity recorded in LogMAR units. Dashed lines represent a change in visual acuity of ± 0.2 LogMAR unit (two lines by Snellen visual acuity).

ate or multivariate analysis. When the analysis was performed without regard for the retinopathy status in the fellow eye, there was a significant association between increased retinopathy in the operated-on eye and female gender. All 13 women in this study had increased retinopathy in the operated-on eye, whereas only four of eight men had increased retinopathy (chi-square analysis, P = .005).

By univariate analysis, three variables (the visual acuity measured by the Potential Acuity Meter, treatment with oral hypoglycemic agents, and the body mass index for females) were predictive of the final visual acuity. The visual acuity measured by the Potential Acuity Meter correlated well with the final visual acuity (Spearman rank correlation = 0.64; P = .0046). The postoperative visual acuity was within two lines of the visual acuity predicted by the Potential Acuity Meter in 11 of 18 eyes (61%). Visual acuity was more than two lines worse than predicted in five eyes, and more than two lines better than predicted in two eyes (Fig. 4). Patients treated with oral hypoglycemic agents had a significantly worse final visual acuity than those not treated with oral hypoglycemic agents (Mann-Whitney U; P = .035). The average final visual acuity was 0.90 by LogMAR (20/160 by Snellen) among patients treated with oral agents, whereas it was 0.38 by LogMAR (20/50 by Snellen) among patients treated with insulin. Obesity in women, as measured by the body mass index, was predictive of worse visual outcome (Mann-Whitney U; P = .021). In contrast, there was not a statistically significant association between obesity and visual outcome among men. On multivariate analysis, after adjustment for age, gender, months of follow-up, body mass index, and use of oral hypoglycemic agents, only one variable, the preoperative visual acuity measured by Potential Acuity Meter, was associated with the final visual acuity (P = .019).

Discussion

In this study we found that diabetic retinopathy progresses frequently in patients undergoing extracapsular cataract extraction and posterior chamber intraocular lens implantation. We and others have previously suggested that removal of the lens contributes to worsening of diabetic retinopathy in the operated-on eye.[6-8] In the current study we found that this phenomenon occurs in a large proportion of patients with preexisting nonproliferative diabetic retinopathy; progression occurred in the operated-on eye alone in seven of 19 patients (37%), whereas it never occurred in the fellow eye alone. It is conceivable that a preoperative dif-

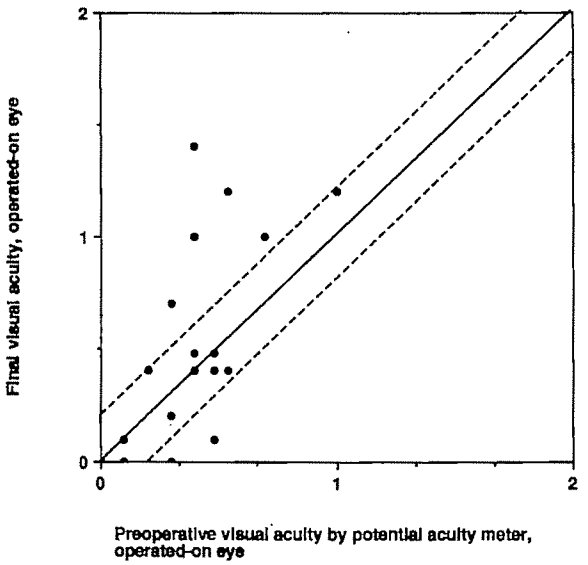


Fig. 4 (Jaffe and associates). Preoperative visual acuity measured by Potential Acuity Meter in operated-on eye compared to corresponding final visual acuity in operated-on eye. Visual acuity recorded in LogMAR units. Dashed lines represent a change in visual acuity of ± 0.2 LogMAR unit.

ference in the rate of retinopathy progression would be reflected by asymmetric retinopathy progression postoperatively. For example, if acceleration of retinopathy progression was associated with the presence of cataract, then this trend for accelerated retinopathy progression would be expected to continue postoperatively. We had insufficient preoperative data to assess the rate of retinopathy progression before cataract extraction; however, regardless of the rate of retinopathy progression preoperatively, the observation that cataract extraction is associated with accelerated retinopathy progression postoperatively remains valid.

In contrast to our findings, in a retrospective study, Sebestyen[5] found that progression of retinopathy in the operated-on eye occurred concurrently with progression in the fellow eye. These results led him to conclude that intraocular lens implantation was not related to retinopathy progression. Because the study of Sebestyen was retrospective, he was unable to determine the true incidence of worsening of retinopathy. Furthermore, an objective measure of worsening of retinopathy was not provided, and only five patients who underwent extracapsular cataract extraction and posterior chamber lens implantation developed retinopathy progression. Thus, the study methods probably were not sufficiently sensitive to detect relative differences in retinopathy progression between the two eyes. In a separate retrospective study, Pollack, Dotan, and Oliver[8] showed that retinopathy progressed in 38.2% of operated-on eyes within one year of cataract extraction, but in only 12.8% of fellow eyes. However, the retrospective nature of the study, the inclusion of patients without preexisting retinopathy, and the inclusion of patients who underwent intracapsular cataract extraction or extracapsular cataract extraction without placement of an intraocular lens preclude meaningful comparisons between the data reported by Pollack, Dotan, and Oliver[8] and our data. Alpar[11] showed that increased retinopathy occurred in 20% of eyes on which extracapsular cataract extraction and placement of an intraocular lens in the ciliary sulcus were performed and in only 1.7% of eyes that had extracapsular cataract extraction and placement of an intraocular lens within the capsule. It is not possible to determine the incidence of progression of nonproliferative retinopathy from that study, however, because patients without preoperative diabetic retinopathy were combined with those with retinopathy in the analysis. Additionally, no information regarding retinopathy in the fellow eye was provided, and thus it is not possible to determine the incidence of asymmetric retinopathy progression.

In most cases, retinopathy progression was characterized by worsening of nonproliferative retinopathy without the development of proliferative disease. In four patients, progression in the operated-on eye was characterized by increased macular edema and proliferative diabetic retinopathy, and proliferative disease progressed similarly in two fellow eyes. We did not observe progression to proliferative diabetic retinopathy in our previous series.[6] The longer follow-up in the current study could account for the appearance of proliferative diabetic retinopathy. Other authors have similarly described progression to proliferative diabetic retinopathy in patients undergoing extracapsular cataract extraction and posterior chamber lens implantation.[2,8,12] Because of the small numbers of patients in each of these studies, however, it was not possible to determine definitively whether cataract extraction contributed to progression of proliferative diabetic retinopathy.

The mechanism by which cataract extraction contributes to progression of nonproliferative diabetic retinopathy remains to be determined. Surgical trauma may contribute to breakdown of the blood-retinal barrier beyond that nor-

mally present in diabetic patients, leading to the findings of increased macular edema, retinal hemorrhages, and hard exudate. The presence of an intact posterior capsule may offer some protection against retinopathy progression[11]; however, in many cases, retinopathy progresses despite the presence of an intact posterior capsule. Previously, we found that retinopathy progressed in six eyes with an intact posterior capsule.[6] Similarly, other investigators have observed asymmetric retinopathy progression in eyes without a capsular break.[2,7,8,12] None of the patients in our current study had a capsular rent at the time of cataract extraction and there was not a significant difference in retinopathy among the patients who underwent YAG capsulotomy postoperatively compared to those who did not.

The results of our current study confirm that patients with preexisting nonproliferative diabetic retinopathy have a worse visual prognosis than those without retinopathy.[1-3] In diabetic patients without retinopathy, up to 90% will achieve a final visual acuity of 20/40 or better. In our study, although most patients had an improvement in visual acuity, only 11 of 21 (52%) had a final visual acuity of 20/50 or better, and only three achieved a visual acuity of 20/25 or better. In most patients, final visual acuity was limited by macular edema. We previously found that the final visual acuity was actually worse than the preoperative visual acuity in six of eight patients, and only one patient achieved a final visual acuity of 20/50.[6] Because that study was retrospective, selection bias probably contributed to the extremely poor visual acuity.

In our current study, all operated-on eyes but one received a posterior chamber intraocular lens; however, we did not specifically address the relationship between the type of posterior chamber intraocular lens inserted and visual outcome and progression of retinopathy. Most eyes required postoperative laser photocoagulation for clinically significant macular edema or proliferative diabetic retinopathy. Furthermore, a subgroup of patients who undergo extracapsular cataract extraction and posterior chamber intraocular lens implantation probably will subsequently benefit from a vitreoretinal surgical procedure for complications related to the development of proliferative diabetic retinopathy or to macular edema caused by vitreous traction. Placement of a posterior chamber intraocular lens that facilitates laser photocoagulation or a vitreoretinal surgical procedure would thus be desirable. To this end, as previously suggested,[13] we recommend insertion of a lens without positioning holes and with a 7-mm optic.

We evaluated several variables to identify those factors that were associated with progression of retinopathy and those that predicted final visual acuity. Women had a significantly increased risk of retinopathy in the operated-on eye compared to men; however, women were not more likely to develop asymmetric progression of retinopathy. Furthermore, we were unable to establish an association between other risk factors and asymmetric progression of retinopathy. The number of patients in this series was relatively small; with a larger database, we probably would have identified additional statistically significant factors predictive of asymmetric retinopathy progression.

There was a good correlation between the preoperative visual acuity measured by the Potential Acuity Meter and the final postoperative visual acuity. Therefore, the Potential Acuity Meter yields useful prognostic information in addition to that provided by the presence or absence of retinopathy. Other variables provide further information that helps to predict final visual acuity; patients treated with oral hypoglycemic agents had a worse visual prognosis than those treated with insulin and overweight women had a worse visual prognosis than those with normal body weight. The reasons for these associations are unclear. Although the observed associations may have been caused by chance, the high degree of correlation (for example, Spearman correlation coefficient = 0.63 for overweight women) and the statistically significant results indicate that these relationships may be important. Furthermore, none of the other variables independently predicted final visual acuity or retinopathy progression on multivariate analysis, indicating that other factors may be involved. There were trends that suggested associations between certain variables and final visual acuity. For example, on the average, the final visual acuity was more than two lines worse among women compared to men; however, this difference was not statistically significant. As discussed previously, with a larger sample size, we probably would have identified additional predictive factors.

Our study was not specifically designed to evaluate the relationship between the degree of nonproliferative diabetic retinopathy present

preoperatively and the rate of retinopathy progression and the final visual acuity postoperatively. However, the patients with the least amount of preoperative retinopathy did not have accelerated retinopathy progression postoperatively, and tended to have a favorable visual outcome. Although the small number of patients and the study design do not permit definitive conclusions, the results suggest that after cataract extraction, patients with minimal or mild retinopathy may have a similar outcome to diabetic patients without retinopathy. Many more patients with minimal to mild retinopathy will need to be studied to confirm this observation.

In our study, preoperative focal laser photocoagulation caused resolution of clinically significant macular edema in most cases, but did not prevent recurrence of clinically significant macular edema postoperatively. Although the Early Treatment Diabetic Retinopathy Study showed a treatment benefit for diabetic patients with clinically significant macular edema, the study did not discriminate between patients who underwent cataract extraction and those who did not.[9] The exact criteria for treatment in the subgroup of patients who undergo cataract extraction remain to be defined. Furthermore, because cataract extraction accelerates nonproliferative diabetic retinopathy in many patients, it may be necessary to treat patients who develop macular edema after cataract extraction more promptly than unoperated-on patients.

On the basis of the results of this study, we offer the following recommendations. All diabetic patients who are scheduled to undergo an extracapsular cataract extraction and posterior chamber intraocular lens implantation should have a comprehensive medical and ophthalmic examination including a detailed retinal examination before cataract extraction. Measurement of visual acuity with the Potential Acuity Meter should be considered to provide additional prognostic information. Diabetic patients should be advised that if they have preoperative nonproliferative diabetic retinopathy, their visual prognosis is significantly worse than if no retinopathy is present. If the patient is also being treated with oral hypoglycemic agents, there is an added risk for poor visual outcome. The patient should be informed that if nonproliferative diabetic retinopathy is present preoperatively, up to 37% of patients will develop progression of retinopathy specifically related to the cataract extraction. Furthermore, because only a few patients had a final visual acuity in the operated-on eye that was significantly better than that of the fellow eye, it is unclear whether the risks of cataract extraction in this group outweigh the potential benefits. For many patients with preexisting nonproliferative diabetic retinopathy, it may be prudent to consider delaying cataract extraction until the cataract is more visually significant.

In addition to providing useful prognostic information, a detailed retinal examination will assist in the identification of patients who would be candidates for preoperative laser photocoagulation or in the early postoperative period. Because we found that extracapsular cataract extraction and intraocular lens implantation accelerate retinopathy progression in a high proportion of patients, we recommend that all patients with preoperative nonproliferative diabetic retinopathy undergo a detailed postoperative retinal examination within the first three months of cataract extraction. These recommendations differ from those for diabetic patients with nonproliferative retinopathy who do not undergo cataract extraction, in whom retinal examinations at six- to 12-month intervals may suffice (The American Academy of Ophthalmology Quality of Care Committee Retina Panel: Preferred Practice Patterns in Diabetic Retinopathy, 1989, p. 6).

Patients with clinically significant macular edema or proliferative diabetic retinopathy should undergo prompt laser photocoagulation as recommended by the Early Diabetic Retinopathy Treatment Study[8,14] and Diabetic Retinopathy Study.[15] In some instances of retinal thickening, it may be difficult to distinguish pseudophakic cystoid macular edema from diabetic macular edema. In these cases, the presence of increasing hemorrhages and lipid deposits suggest that the edema is at least partly related to the diabetes; it would be reasonable to consider laser photocoagulation of these eyes. In contrast, if retinal thickening is present, hemorrhages and lipid deposits have not changed significantly, and fluorescein angiography shows a petalloid pattern of foveal hyperfluorescence characteristic of pseudophakic cystoid macular edema, then delay of laser photocoagulation for three to four months should be considered to allow for spontaneous resolution. Finally, as discussed previously, placement of a posterior chamber intraocular lens with a 7-mm optic and no positioning holes may facilitate visualization during laser

photocoagulation and vitreoretinal surgical procedures.

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OPHTHALMIC MINIATURE

He arranged the reins to her satisfaction, and, looking up at her, she saw his eyes for the first time from beneath the brim of his hat. They were strange eyes, transparent like glass, and so pale in colour that they seemed near to white; a freak of nature she had never known before. They fastened upon her, and searched her, as though her very thoughts could not be hidden, and Mary felt herself relax before him, and give way; and she did not mind.

Daphne du Maurier, *Jamaica Inn*
London, Victor Gollancy Ltd., 1949, p. 70

Efficacy of Fluid-Air Exchange for Postvitrectomy Diabetic Vitreous Hemorrhage

Daniel F. Martin, M.D., and Brooks W. McCuen II, M.D.

We reviewed the records of 33 fluid-air exchanges to assess the efficacy of fluid-air exchange in the management of recurrent vitreous cavity hemorrhage after vitrectomy for proliferative diabetic retinopathy. Fluid-air exchange alone was successful in clearing the vitreous cavity in ten of 20 eyes after a mean of 1.5 exchanges per eye. Repeat vitrectomy was required in the remaining ten eyes and anterior hyaloidal fibrovascular proliferation was frequently found. Hemorrhages that occurred in the late postoperative period (more than nine months) appeared more likely to be successfully treated with fluid-air exchange alone. Failure of the initial fluid-air exchange to induce clearing immediately after the procedure appeared to be associated with subsequent exchange failures and need for surgical intervention. Complications from the exchange procedure were infrequent with the development of peripheral retinal detachment in one eye. Our current recommendation for nonclearing recurrent postvitrectomy diabetic vitreous hemorrhage is to perform a fluid-air exchange, provided no other high-risk characteristics are present. If clearing occurs in the immediate postexchange period but rebleeding occurs at a later period, we recommend a second fluid-air exchange. If clearing does not occur in the immediate postexchange period, we recommend proceeding directly to revision of vitrectomy.

Fluid-air and fluid-gas exchange are well-established techniques that are performed for a variety of indications after vitreous surgery. These procedures have been used to extend the duration of retinal tamponade,[1] to remove blood from the vitreous cavity in nonclearing persistent or recurrent vitreous hemorrhage,[1-3] to initiate tamponade in recurrent retinal detachment,[1] and to obtain fluid for culture or histologic evaluation, or both, in cases of endophthalmitis or large cell lymphoma.[4] The role of fluid-air exchange in the management of postvitrectomy diabetic vitreous hemorrhage would at first appear obvious: to clear the visual axis to improve visual acuity, to improve visualization of the posterior pole for better postoperative treatment, and to facilitate additional laser photocoagulation when required. It has been our observation, however, and that of others,[2,3] that a significant number of these eyes continue to rebleed. The site of rebleeding is frequently not identified and the possibility of anterior hyaloidal fibrovascular proliferation is often raised. Eyes with anterior hyaloidal fibrovascular proliferation have a guarded prognosis and aggressive surgical intervention is usually required.[5] Because fluid-air exchange itself does not directly address the source of bleeding, we were interested in knowing the impact of this procedure on the longitudinal course of an eye with a postvitrectomy diabetic vitreous hemorrhage. More specifically, we wondered how frequently fluid-air exchange was the final or definitive procedure for eyes with postvitrectomy diabetic vitreous hemorrhage, or whether formal surgical revision ultimately was required in most cases. To answer this question, we reviewed the postoperative records of all diabetic patients who underwent fluid-air exchange for recurrent diabetic vitreous hemorrhage after vitrectomy.

Patients and Methods

The medical records of all diabetic patients who underwent fluid-air exchange for recurrent postvitrectomy diabetic vitreous hemorrhage were reviewed to determine patient charac-

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From the Department of Ophthalmology, Duke University Eye Center, Durham, North Carolina. Dr. Martin was a 1990–1991 Heed Ophthalmic Fellow.

Reprint requests to Brooks W. McCuen II, M.D., Duke University Eye Center, Box 3802, Durham, NC 27710.

teristics, duration of diabetes, adequacy of preoperative laser treatment, time to recurrent postvitrectomy diabetic vitreous hemorrhage, best postexchange visual acuity, incidence of rebleeding, number of repeated fluid-air exchanges required, incidence and indications for formal surgical revision, final status of the lens, and final visual and anatomic results. Recurrent postvitrectomy diabetic vitreous hemorrhage was defined as marked clearing of the visual axis postoperatively followed by a sudden, severe change in visualization of the posterior segment secondary to new vitreous hemorrhage. Persistent postvitrectomy diabetic vitreous hemorrhage was defined as residual hemorrhage that failed to clear in the immediate postoperative period. Eyes on which fluid-air exchange was performed for persistent postvitrectomy diabetic vitreous hemorrhage were excluded from this study.

Standard three-port vitrectomy had been performed on all eyes for the following diagnoses: nonclearing vitreous hemorrhage (11 eyes), traction macular detachment (eight eyes), macular-threatening traction retinal detachment (three eyes), and combined traction/rhegmatogenous retinal detachment (two eyes). Twenty-three of 24 eyes had received panretinal photocoagulation preoperatively and in most cases, the degree of photocoagulation was considered extensive (> 3,000 spots).

The method of fluid-air exchange has previously been described,[3,6] but is outlined as follows. After retrobulbar or topical anesthesia, or both, an eyelid speculum was placed and a 10% povidone iodine solution was instilled in the eye. The patient was placed in a lateral decubitus position with the temporal corneoscleral limbus of the eye on which exchange was to be performed in the most dependent position. A 10-ml syringe with a 25-gauge ⅝-inch needle was partially filled with 5 cc of sterile air. The needle was inserted temporally through the pars plana, 3.5 mm posterior to the corneoscleral limbus, and was directed posteriorly toward the optic nerve to avoid damage to the lens. A small amount of air was injected into the vitreous cavity and an equal volume of bloody fluid was sequentially aspirated into the syringe. The exchange was continued with alternating small injections of air and aspirations of an equal amount of fluid. The needle tip was maintained beneath the air-fluid meniscus by slowly withdrawing it from the globe until the exchange was completed. The intraocular pressure was measured and the posterior segment was inspected to assess the adequacy of exchange. A light, sterile dressing was applied. The patient was instructed to maintain a face-down position and then allowed to return home. Follow-up visits were typically scheduled for one day, one week, and one month postoperatively, but occasionally varied depending on the patient's postoperative course.

Treatment of eyes with fluid-air exchange alone was considered successful if the vitreous cavity remained clear for a minimum of six months after the last exchange procedure. Formal surgical intervention was considered a study endpoint and treatments of these eyes were considered fluid-air exchange failures. Additional follow-up for these eyes was not required.

Results

Between October 1984 and January 1991, 33 fluid-air exchanges were performed on 24 eyes of 23 patients for recurrent postvitrectomy diabetic vitreous hemorrhage. Fifteen patients were men and eight were women. The average age was 45 years (range, 26 to 82 years). Twenty-two eyes were phakic and two were pseudophakic. The mean duration of diabetes was 20.6 years (range, 13 to 33 years). Mean follow-up for eyes treated with fluid-air exchange alone was 37 months (range, six to 75 months; median, 30 months).

The previtrectomy visual acuity, best postvitrectomy visual acuity, visual acuity at the time of recurrent postvitrectomy diabetic vitreous hemorrhage, and final visual acuity were determined for each patient (Fig. 1). The visual acuity for all patients at the time of postvitrectomy diabetic vitreous hemorrhage was hand motions or light perception. Final visual acuity was less than 20/200 in nine eyes and was attributed to the original traction macular detachment (five eyes) or to macular ischemia (four eyes). Four eyes developed recurrent vitreous cavity hemorrhage after a successful fluid-air exchange, but either were lost to follow-up (two eyes), the patient refused further intervention (one eye), or the patient died before the recommended treatment (one eye). One method of handling these eyes statistically would be to consider them as fluid-air exchange failures. However, it is not clear that treatment with fluid-air exchange alone would have failed in these eyes. Treatment in two of these eyes

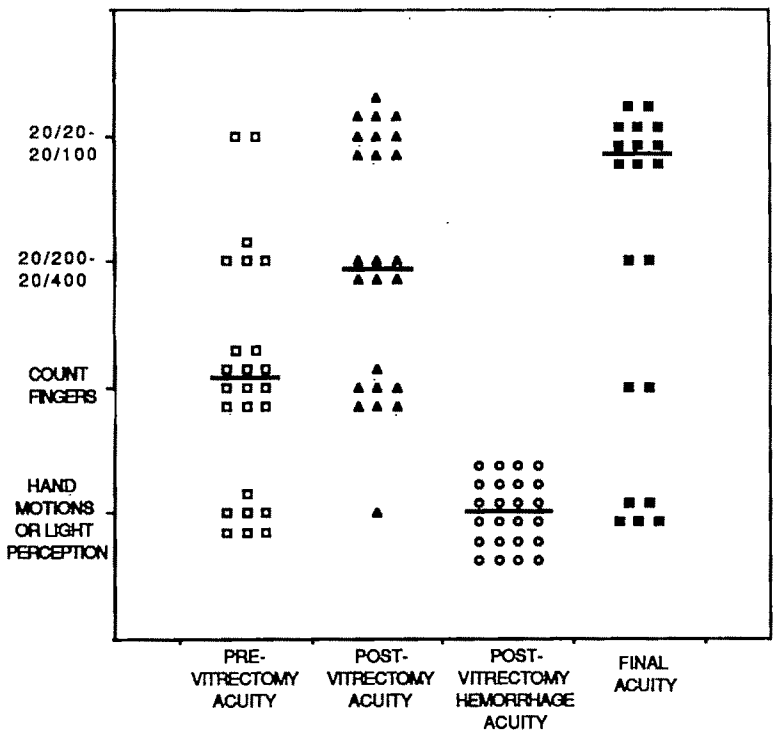


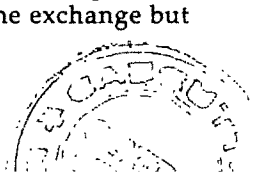
Fig. 1 (Martin and McCuen). Previtrectomy visual acuities (open squares), best postvitrectomy visual acuities (filled triangles), visual acuities at the time of postvitrectomy diabetic vitreous hemorrhage (open circles), and final visual acuities (filled squares) are shown. Horizontal bars represent median visual acuity for each group.

appeared to be successful without surgical intervention two months after recurrent vitreous cavity hemorrhages (one eye was clearing spontaneously, the other eye was doing well after a second fluid-air exchange), but no long-term follow-up data are available. In the remaining two eyes, additional treatment (fluid-air exchange) was recommended, but the patient either refused or died before treatment could be rendered. Rather than attempt to extrapolate data from incomplete records regarding the final visual result and ultimate success of the fluid-air exchange procedure in these eyes, we excluded all four eyes from the remainder of the study.

Fluid-air exchange alone, without subsequent formal surgical revision, was successful in clearing the vitreous cavity in ten of 20 eyes. Six eyes required a single exchange, three eyes required two exchanges, and one eye required three exchanges (mean, 1.5 exchanges per eye). Repeat vitrectomy was ultimately required to clear the vitreous cavity in the remaining ten eyes. Indications for surgical intervention included rebleeding after two or more fluid-air exchanges (four eyes), rebleeding with retinal detachment (one eye), rebleeding with progressive iris neovascularization (three eyes), and rebleeding with deterioration of the fellow eye (two eyes). Final visual acuities were rank ordered for each group and the median final visual acuity for those eyes treated with fluid-air exchange alone was 20/40; for those eyes that required vitrectomy, the median final visual acuity was 20/70.

The median time interval from initial vitrectomy to first postvitrectomy diabetic vitreous hemorrhage was six weeks (range, one to 108 weeks). Thirteen hemorrhages occurred in the early postoperative period (zero to three months), two occurred three to nine months postoperatively, and five occurred in the late postoperative period (more than nine months). Four of five hemorrhages (80%) that occurred in the late postoperative period (more than nine months) were successfully treated with fluid-air exchange alone, as opposed to six of 15 hemorrhages (40%) that occurred within the first nine months postoperatively ($P = .3$; Fisher's exact test, two-tailed).

After the initial fluid-air exchange, dense vitreous cavity hemorrhage was present at some point during the postexchange course in 16 of 20 eyes (80%). In ten eyes, dense hemorrhage was present immediately after resolution of the air bubble. Eight of these eyes ultimately required surgical intervention, usually after an additional one or more failed fluid-air exchanges. In the remaining six eyes, clearing of the vitreous cavity occurred after the exchange but



was followed by recurrent, severe vitreous cavity hemorrhage at a median time interval of eight weeks (range, two to 90 weeks). Two eyes spontaneously cleared, two eyes required one additional fluid-air exchange, and only two (33%) eyes ultimately required vitrectomy. Although failure of the initial fluid-air exchange to induce clearing of the vitreous cavity immediately after the procedure appeared to predict the necessity of further surgical intervention, this observation did not achieve statistical significance (80% vs 33%; P = .12, Fisher's exact test, two-tailed).

Complications that could be directly attributed to the fluid-air exchange were infrequent. One eye developed a peripheral retinal detachment shortly after an exchange procedure, which was successfully repaired with a scleral buckle. Of the eyes for which complete records were available, 18 of 20 were phakic at the time of the initial exchange. Thirteen lenses were clear, three had early posterior subcapsular opacities, and two had early nuclear sclerosis. In only one case of the 29 fluid-air exchanges performed on phakic eyes was an increase in lens opacity noted one month after the exchange. At the time of last follow-up, seven lenses remained clear, three were unchanged from their baseline opacity, three had remained clear but were removed intraoperatively for anterior hyaloidal fibrovascular proliferation, and three had initially remained unchanged after fluid-air exchange, but then progressed six months to three years after additional vitreoretinal surgery. In the remaining two eyes, increased lens opacity (posterior subcapsular cataract in one eye, nuclear sclerosis in the other eye) was present six months after the final fluid-air exchange. In both of these eyes, two exchange procedures had been performed.

Discussion

Vitreous cavity hemorrhage after vitrectomy for proliferative diabetic retinopathy is a common cause of postoperative morbidity. Hemorrhage in the postoperative period has traditionally been grouped into the following two categories: (1) persistent or residual postvitrectomy diabetic vitreous hemorrhage defined as blood remaining in the vitreous cavity on the first postoperative day, and (2) recurrent postvitrectomy diabetic vitreous hemorrhage defined as rebleeding after a period of marked clearing of the vitreous cavity. Schachat and associates[7] and Novak and associates[8] described residual vitreous hemorrhage present on the first postoperative day in 75% and 63% of eyes, respectively. The degree of hemorrhage was considered mild or moderate in most cases and usually cleared rapidly within six to nine weeks. The reported incidence of recurrent postvitrectomy diabetic vitreous hemorrhage has ranged from 23% to 60%.[7-8] When spontaneous clearing occurred, it usually did so in seven to 11 weeks. The rate of clearing and the incidence of total clearing was greater in aphakic eyes than in phakic eyes, probably because of the increased access of blood to the anterior chamber and trabecular outflow channels.[8] It is not surprising, then, that phakic eyes have more frequently required therapeutic intervention.[3] In our series, 22 of 24 eyes were phakic, which supports this observation.

We restricted this study to eyes on which fluid-air exchange was performed for recurrent postvitrectomy diabetic vitreous hemorrhage. In our experience, a decision regarding therapeutic intervention was much more frequently required for this condition than for persistent postvitrectomy diabetic vitreous hemorrhage. The variables to be considered in the decision process were also quite different. Rebleeding after a period of clearing implies an increased likelihood of active neovascularization, including the possibility of anterior hyaloidal fibrovascular proliferation. Eyes with anterior hyaloidal fibrovascular proliferation have a guarded prognosis and early, aggressive surgical intervention has been recommended.[5] Fluid-air exchange necessarily delays that surgical intervention. However, it is usually not known whether an eye actually contains anterior hyaloidal fibrovascular proliferation and, therefore, whether vitrectomy would be required, at the time a decision is made. It has been our practice to perform up to two (and in some cases three) fluid-air exchanges for recurrent hemorrhage, provided that other high-risk characteristics (neovascularization of the iris, recurrent retinal detachment, or other indications of anterior hyaloidal fibrovascular proliferation) are not present. Whether this delay inherent in our practice results in a poorer visual and anatomic outcome was of considerable interest to us. To answer this question definitively, a prospective study would be required. However, several observations may be made from the retrospective review of our data.

In our series, fluid-air exchange alone was

successful in inducing long-term clearing of the vitreous cavity in ten of 20 cases after a mean of 1.5 exchanges per eye. Eyes that developed postvitrectomy diabetic vitreous hemorrhage more than nine months after their initial surgical procedure appeared to be among those eyes most likely to benefit from fluid-air exchange. Four of five of these eyes (80%) were successfully treated with fluid-air exchange alone, as opposed to six of 15 hemorrhages (40%) that occurred within the first nine months postoperatively. Although this observation was without statistical significance, the number of eyes involved in this study was small. Intuitively, this observation would seem to make sense. Proliferative diabetic retinopathy may enter a relatively dormant state after adequate photocoagulation. It follows then, that if an eye remains clear for nine months to two years after vitrectomy and adequate photocoagulation, it would imply that the initial source of the bleeding (neovascularization) has been sufficiently treated. If rebleeding then occurs, it would be less likely to be caused by a fulminant disease process such as anterior hyaloidal fibrovascular proliferation.

The inherent delay in surgical intervention caused by one or more fluid-air exchanges did not appear to negatively affect final visual outcome. Median final visual acuity for eyes that ultimately required surgical intervention was 20/70 and was not significantly different from the final visual outcome for eyes treated with fluid-air exchange alone (median, 20/40) ($P > .05$, Wilcoxon rank sum). Although repeating a fluid-air exchange did not appear to affect the final result negatively, it also did not appear to offer additional benefit to those eyes that did not have marked clearing in the immediate period after the initial exchange. Eight of these ten eyes ultimately required surgical intervention, usually after an additional one or more failed fluid-air exchanges, as opposed to two of six eyes (33%) that had marked clearing in the immediate postexchange period ($P = .12$, Fisher's exact test, two-tailed). We believe that rebleeding in the immediate postexchange period suggests a more aggressive disease, such as anterior hyaloidal fibrovascular proliferation, that would not be adequately treated with additional fluid-air exchanges alone. In our series, anterior hyaloidal fibrovascular proliferation was present in all four of the eyes on which lensectomy and vitreous base dissection were performed and was strongly suspected in the remaining six eyes on which repeat vitrectomy was performed, but were maintained phakic. Retinal cryotherapy or indirect laser photocoagulation of the peripheral retina out to the ora serrata was performed for 360 degrees in these six eyes, rather than vitreous base dissection, in an attempt to salvage the lens. No further vitreous cavity hemorrhages occurred after using this technique (mean follow-up, six months).

Significant untoward effects from the fluid-air exchange procedure were infrequent. In the series described by Han and associates,[2] ten of the 17 phakic eyes (59%) on which fluid-air exchange was performed developed new or had worsening of their preexisting posterior subcapsular cataracts. This differed from our experience. In our series, a total of five of 18 eyes (28%) developed lens opacities during the postexchange period, and in only one of 18 eyes (6%) could an argument be made that the opacity was related to the fluid-air exchange itself, rather than to other known cataractogenic variables. Three of the five eyes initially remained unchanged after fluid-air exchange but then progressed six months to three years after additional vitreoretinal surgery. Because the incidence of cataract formation after diabetic vitrectomy alone has ranged from 22% to 32%,[7,10,11] it is unclear precisely what role the fluid-air exchange had in the development of lens changes in these eyes. Of the remaining two eyes, one developed nuclear sclerosis three years after the second (and last) fluid-air exchange. The typical lens opacity associated with the use of intravitreal gases is posterior subcapsular feathering, and when it occurs, it is usually apparent in the immediate postexchange period.[12] The features and time course of the opacity in this eye are perhaps more characteristic of the lens changes seen after vitrectomy rather than the lens changes usually attributed to fluid-air or fluid-gas procedures. In the final eye, posterior subcapsular feathering was noted within the first month after a second (and final) fluid-air exchange and slowly progressed without any additional vitreoretinal procedures. The time course and characteristics of this lens change seem to be consistent with a fluid-air exchange–induced opacity. A further difference between our series and that described by Han and associates[2] is the appearance in their series of a new onset of posterior capsular opacities in eight eyes immediately after fluid-air exchange. In only one case of the 29 fluid-air exchanges performed on phakic eyes in our series was an increase in lens opaci-

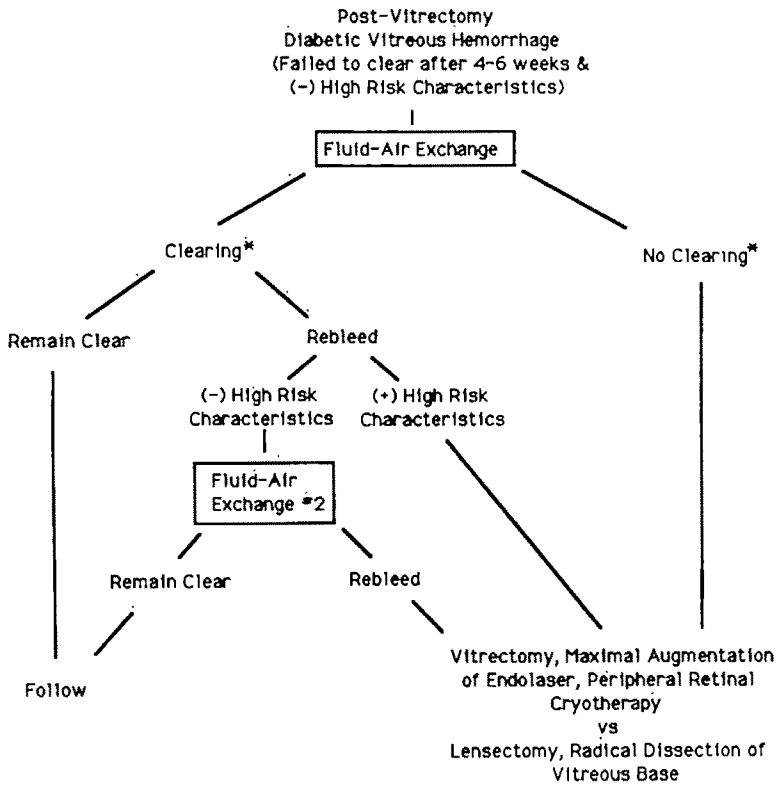


Fig. 2 (Martin and McCuen). Algorithm for the management of postvitrectomy diabetic vitreous hemorrhage. High-risk characteristics (+ indicates present; − indicates absent) are anterior hyaloidal fibrovascular proliferation or progressive iris neovascularization. Asterisks indicate clearing in the immediate postexchange period.

ty noted within the first month after the exchange. The reason for this difference is not immediately apparent. Han and associates[2] used a two-needle injection/aspiration technique that may, as they state, result in a slightly more complete fill than the single-needle push-pull technique that we used. Lens opacities have been reported to most likely occur when the gas bubble occupies more than two thirds of the vitreous volume.[13-15] A more complete fill, then, from the two-needle method may account for the difference in our series. However, the face-down positioning encouraged by both groups and the rapid absorption of air from the vitreous cavity would tend to diminish the degree of air-lens contact and, therefore, tend to minimize any small differences in the degree of filling between these two techniques.

On the basis of the results of this study, our present recommendation for recurrent postvitrectomy diabetic vitreous hemorrhage that fails to clear over a four- to six-week period is to perform a fluid-air exchange, provided no high-risk characteristics (anterior hyaloidal fibrovascular proliferation, progressive iris neovascularization) are present (Fig. 2). If clearing occurs in the immediate postexchange period but rebleeding occurs at a later period, we recommend a second fluid-air exchange, again provided no other high-risk characteristics are present. If clearing does not occur in the immediate postexchange period, we recommend proceeding directly to revision of vitrectomy with maximal augmentation of endolaser photocoagulation and administration of peripheral retinal cryotherapy or peripheral indirect laser photocoagulation. In cases associated with severe anterior hyaloidal fibrovascular proliferation, lensectomy and radical dissection of the vitreous base should also be considered.

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Immunohistochemical and Histochemical Properties of Surgically Excised Subretinal Neovascular Membranes in Age-related Macular Degeneration

Hans E. Grossniklaus, M.D., Jose A. Martinez, M.D., Vonita B. Brown, H. Michael Lambert, M.D., Paul Sternberg, Jr., M.D., Antonio Capone, Jr., M.D., Thomas M. Aaberg, M.D., and Pedro F. Lopez, M.D.

The immunohistochemical and histochemical properties of 16 surgically excised subretinal neovascular membranes from 16 patients with age-related macular degeneration were studied. Primary antisera to c-retinaldehyde-binding protein; leukocyte common antigen; factor VIII-related antigen; S-100 protein; glial fibrillary acid protein; muscle-specific actin; neuron-specific enolase; collagen types I, II, III, IV, and V; laminin; and fibronectin were used for immunohistochemical characterization of the membranes. Histochemical staining for lipid and mucopolysaccharide was performed. The results of the staining in conjunction with histologic examination showed the cellular components of the membranes to be composed of retinal pigment epithelium, inflammatory cells, vascular endothelium, glial cells, myofibroblasts, photoreceptor cells, and fibrocytes. The extracellular matrix of the membranes contained collagen types I, III, IV, and V; fibronectin; laminin; mucopolysaccharide; and lipid. These findings are consistent with the concept that subretinal neovascular membranes in age-related macular degeneration are composed of localized intra-Bruch's membrane granulation tissue proliferation associated with diffuse drusen.

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From the Departments of Ophthalmology (Drs. Grossniklaus, Martinez, Lambert, Sternberg, Capone, Aaberg, and Lopez, and Ms. Brown) and Pathology (Dr. Grossniklaus), Emory University, Atlanta, Georgia. Dr. Lopez was a 1990–1992 Heed-Knapp Fellow. This study was supported in part by a grant from the Knights Templar Eye Foundation, Inc., Springfield, Illinois (Dr. Grossniklaus) and an unrestricted departmental grant from Research to Prevent Blindness, Inc., New York, New York.

Reprint requests to Hans E. Grossniklaus, M.D., L. F. Montgomery Ophthalmic Pathology Laboratory, Rm. 1603, Emory Eye Center, 1327 Clifton Rd. N.E., Atlanta, GA 30322.

Of the United States population, approximately 9% has age-related macular degeneration.[1] Histopathologic findings suggestive of age-related macular degeneration are found in 33% of postmortem eyes obtained from persons 65 years or older.[2] The clinicopathologic features of age-related macular degeneration have been well documented[3,4] and include drusen, areolar atrophy, subretinal neovascularization, and disciform scar formation. Previous pathologic studies of age-related macular degeneration subretinal neovascularization have described changes occurring in eyes obtained post mortem, often after chronic disease, thus allowing limited examination of the tissue for early changes in the subretinal neovascular membranes.

Recently, surgically excised subretinal neovascular membranes obtained from patients with age-related macular degeneration have become available for pathologic examination.[5-8] Ultrastructural examination of ten membranes performed in our laboratory has previously disclosed the presence of vascular channels, macrophages, fibrocytes, retinal pigment epithelium, erythrocytes, lymphocytes, photoreceptors, myofibroblasts, plasma cells, collagen, fibrin, basal laminar deposit, and fragments of Bruch's membrane.[7] Puklin and associates[8] used immunoelectron microscopy and confirmed the presence of vascular endothelium, fibrocytes, collagen, and additionally found fibronectin in subretinal neovascular membranes obtained from three patients with age-related macular degeneration. To characterize the cellular and extracellular constituents of these

membranes further and to develop an understanding of the tissue response in age-related subretinal neovascularization, we examined the immunohistochemical and histochemical properties of 16 surgically excised subfoveal neovascular membranes. We chose the antisera and histochemical stains to evaluate the membranes on the basis of cellular and extracellular material demonstrated by our previous ultrastructural examination[7] and that of others.[8-10]

Material and Methods

Fresh surgically excised subfoveal neovascular membranes from 16 patients with age-related macular degeneration were snap-frozen to −20 C and ten to 20 serial sections were cut 5 μm thick and placed on poly-l-lysine–coated slides. One slide from each membrane was stained with hematoxylin and eosin.

All membranes were immunostained by using the standard avidin-biotin complex technique.[11] The first eight membranes were stained for leukocyte common antigen (1:500, Dako, Carpinteria, California), S-100 protein (1:400, Dako), neuron-specific enolase (1:400, Dako), glial fibrillary acid protein (1:400, Dako), collagen type I (1:500, courtesy of Robert Swerlick, M.D., Atlanta, Georgia), collagen type IV (1:500, courtesy of Robert Swerlick, M.D.), laminin (1:700, Chemicon, Temecula, California), and fibronectin (1:500, Chemicon). The second eight membranes were immunostained with primary antisera to factor VIII–related antigen (1:100, Dako), c-retinaldehyde–binding protein (courtesy of John Crabb, Ph.D., Lake Placid, New York), muscle-specific actin (1:10,000, Enzo, New York, New York), collagen type II (Chemicon), collagen type III (Biogenex, San Ramon, California), and collagen type V (Calbiochem, La Jolla, California). The slides were bleached with potassium permanganate and hydrobromic acid before application of the antisera to c-retinaldehyde–binding protein and negative bleach controls were prepared. All other slides, including control slides, were not bleached. Endogenous peroxidase activity was blocked by the application of hydrogen peroxide. Nonspecific binding was blocked by application of a universal normal serum. The primary antibody was then applied. Biotinylated antimouse/antirabbit immunoglobulin was applied as a linking reagent, followed by the application of streptavidin, which labeled the antibody. Slides were developed with fresh 3,3′ diaminobenzidine tetrahydrochloride (Sigma, St. Louis, Missouri). The slides were counterstained with hematoxylin. Negative control slides were made by substituting phosphate-buffered saline solution for the primary antisera and positive controls that used skin, skeletal muscle, and normal eye tissues were prepared. Histochemical stains for mucopolysaccharide (alcian blue, pH 1.0 and pH 2.5) and neutral lipid (oil-red-o) were performed on the second eight membranes. Positive controls for the histochemical stains included adrenal gland and umbilical cord tissue.

Results

The membranes were excised from eight men and eight women. The mean age of the patients was 74 years (range, 56 to 85 years). Three membranes were excised from right eyes and 13 were excised from left eyes. The average preoperative and postoperative visual acuity of the patients was 20/200 with a follow-up of three months. The results of the staining of the membranes from the first eight patients were analyzed (Table 1). The general configuration of the membranes was that of fibrovascular tissue subjacent to retinal pigment epithelium. A negative control was used to examine for positive immunostaining (Fig. 1). Occasionally, areas characteristic of diffuse drusen and fragments of the inner aspect of Bruch's membrane were present. The cellular components of the first eight membranes stained for the following antigenic determinants in decreasing order of frequency: leukocyte common antigen, five of eight (63%); glial fibrillary acid protein, three of eight (38%); S-100 protein, three of eight (38%); and neuron-specific enolase, one of eight (13%). Photoreceptor cells served as an internal control in the one membrane that contained neuron-specific enolase–positive cells (Fig. 2). Glial fibrillary acid protein–positive cells often coexpressed S-100 protein and formed monolayers on the membranes or were scattered within the membranes (Fig. 3). Leukocyte common antigen–positive cells were scattered throughout the membranes. Extracellular material was diffusely scattered and stained for collagen type I (Fig. 4), collagen type IV (Fig. 5), laminin (Fig. 6), and fibronectin (Fig. 7) in all of the first eight membranes. Laminin was found only within the membranes compared with fi-

TABLE 1
IMMUNOHISTOCHEMICAL FINDINGS IN SUBRETINAL NEOVASCULAR MEMBRANES IN THE FIRST EIGHT PATIENTS WITH AGE-RELATED MACULAR DEGENERATION

PATIENT NO.	LEUKOCYTE COMMON ANTIGEN	S-100 PROTEIN	NEURON-SPECIFIC ENOLASE	GLIAL FIBRILLARY ACID PROTEIN	COLLAGEN TYPE I	COLLAGEN TYPE IV	LAMININ	FIBRONECTIN
1	Yes	No	No	No	Yes	Yes	Yes	Yes
2	Yes	No	No	No	Yes	Yes	Yes	Yes
3	No	No	Yes	Yes	Yes	Yes	Yes	Yes
4	Yes	Yes	No	No	Yes	Yes	Yes	Yes
5	No	Yes	No	Yes	Yes	Yes	Yes	Yes
6	Yes	No	No	No	Yes	Yes	Yes	Yes
7	No	No	No	No	Yes	Yes	Yes	Yes
8	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes

bronectin, which was scattered within the membranes and present in occasional fragments of associated photoreceptor cells.

The results of the staining of the membranes from the second eight patients were analyzed (Table 2). Similar to the architecture of the first eight membranes, the second set of eight membranes had fibrovascular tissue subjacent to retinal pigment epithelium. A negative control slide was used to evaluate the immunostaining as in the first eight membranes (Fig. 8). Positive immunostaining of the cellular components within the second eight membranes in decreasing order of frequency was as follows: c-retinaldehyde–binding protein, seven of eight (88%) (Fig. 9); factor VIII–related antigen, four of eight (50%) (Fig. 10); and muscle-specific actin, one of eight (13%). The c-retinaldehyde protein–positive cells corresponded to what appeared to be monolayers of retinal pigment epithelium cells and occasional individual cells within the membranes. Factor VIII–positive cells corresponded to vascular endothelium within the membranes. Muscle-specific actin positivity was demonstrated in spindle-shaped cells in one membrane. Extracellular constituents that were present in all of the second eight membranes included mucopolysaccharide and lipid. The extracellular matrix of the membranes stained more intensely with alcian blue at a pH of 1.0 compared with a pH of 2.5, which indicated the presence of sulfated mucopolysaccharides.[12] Lipid that stained with oil-red-o was demonstrated in the cytoplasm of retinal pigment epithelium, in fragments of Bruch's membrane, and diffusely scattered within the membranes (Fig. 11). Collagen type III was present within six of eight (75%) of the membranes (Fig. 12) and collagen type II was not identified within the membranes. All controls

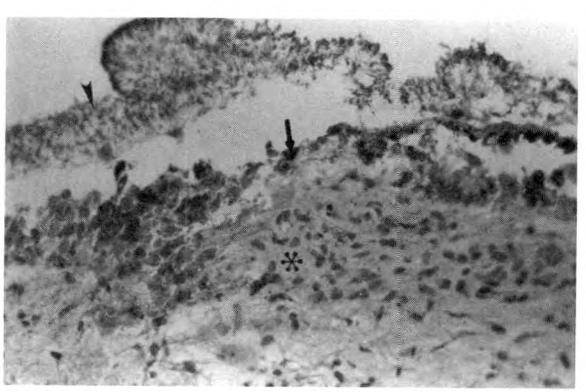


Fig. 1 (Grossniklaus and associates). Patient 3. A negative control illustrates a layer of photoreceptor cells (arrowhead) overlying retinal pigment epithelium (arrow) and a fibrovascular membrane (asterisk) (diaminobenzidine, × 40).

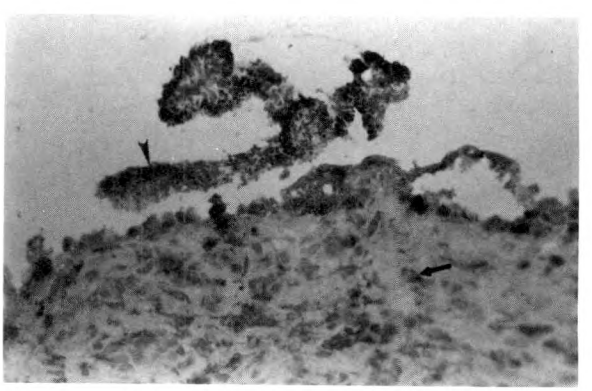


Fig. 2 (Grossniklaus and associates). Patient 3. Neuron-specific enolase positivity is demonstrated in photoreceptor cells (arrowhead) and occasional cells in the stroma (arrow) (diaminobenzidine, × 40).

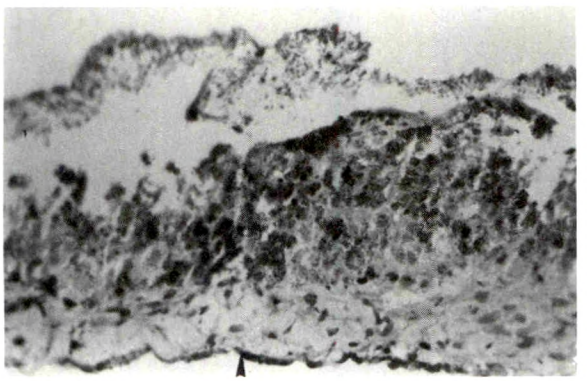


Fig. 3 (Grossniklaus and associates). Patient 3. A monolayer of cells that stains positive for glial fibrillary acid protein (arrowhead) is present on the external surface of the membrane (diaminobenzidine, × 40).

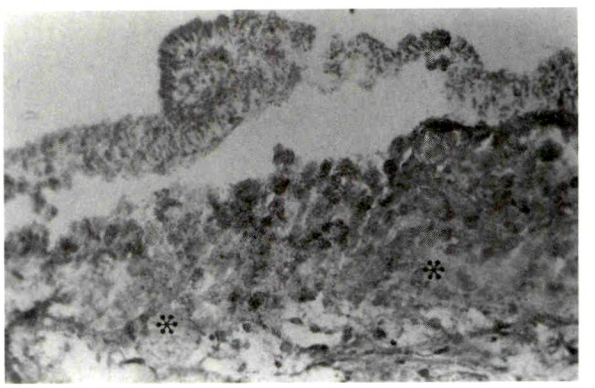


Fig. 4 (Grossniklaus and associates). Patient 3. The extracellular matrix (asterisks) of the membrane stains positive for type I collagen (diaminobenzidine, × 40).

were appropriately positive and negative where expected. The predominant features of two representative membranes were chosen for illustration.

Discussion

The results of this study, in conjunction with our previous ultrastructural findings,[7] are consistent with the concept that the pathogenetic mechanism of subretinal neovascularization in age-related macular degeneration is a nonspecific, stereotypic, localized wound repair response into Bruch's membrane in areas of diffuse drusen. Subretinal neovascularization appears similar to granulation tissue proliferation as seen in other tissues in response to a variety of stimuli.[13-16] The analogy of subretinal neovascularization to granulation tissue proliferation is not precise because immunohistochemical and histochemical staining were not used to examine the precursors of subretinal neovascularization in age-related macular degeneration in this study; however, a comparison of the constituents of subretinal neovascularization with granulation tissue proliferation may be useful. Special stains demonstrated sulfated mucopolysaccharides in the subretinal neovascular membranes in our study, a constituent present in granulation tissue proliferation. The extracellular matrix in granulation tissue first contains type III collagen and fibronectin and is later replaced by type I collagen and increased laminin. These materials were demonstrated in the subretinal neovascular membranes in our study and previous ultrastructur-

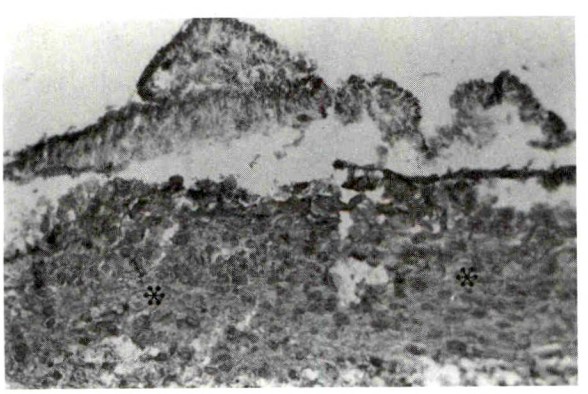


Fig. 5 (Grossniklaus and associates). Patient 3. Type IV collagen diffusely stains in the extracellular matrix (asterisks) of the membrane (diaminobenzidine, × 40).

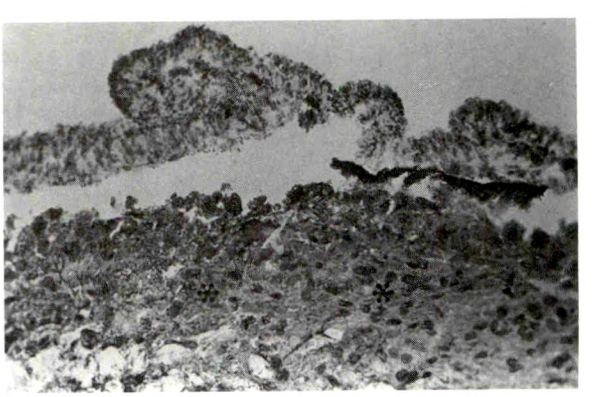


Fig. 6 (Grossniklaus and associates). Patient 3. Stains are positive for laminin diffusely throughout the extracellular matrix (asterisks) of the membrane (diaminobenzidine, × 40).

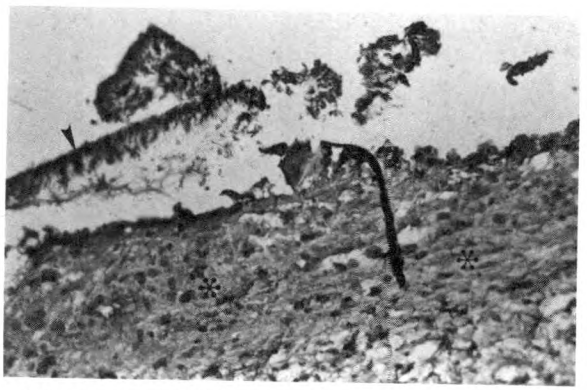


Fig. 7 (Grossniklaus and associates). Patient 3. Fibronectin is diffusely stained in the extracellular matrix (asterisks) of the membrane and in the layer of photoreceptor cells (arrowhead) (diaminobenzidine, × 40).

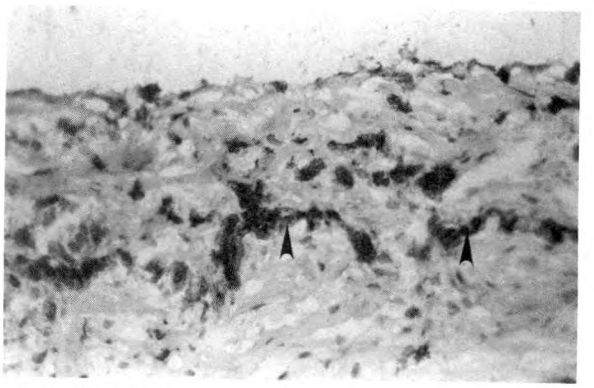


Fig. 8 (Grossniklaus and associates). Patient 12. A negative control demonstrates a layer of retinal pigment epithelium cells (arrowheads) within the membrane (diaminobenzidine, × 40).

al examination of subretinal neovascular membranes from patients with age-related macular degeneration performed in our laboratory.[7] It was impossible to correlate the age of the membranes with the types of collagen present because the length of time the membranes were present was unknown.

The cellular components of the surgically excised subretinal neovascular membranes as determined by immunohistochemical methods in this study included, in decreasing order of frequency, retinal pigment epithelium, inflammatory cells, vascular endothelium, glial cells, myofibroblasts, and photoreceptor cells. Retinal pigment epithelium expressed antigenic determinants to c-retinaldehyde–binding protein in seven of eight of the membranes (88%) in this study. The presence of intracytoplasmic lancet-shaped melanin granules in the cells that stained for c-retinaldehyde–binding protein provided evidence that these cells were retinal pigment epithelium, although it is possible that some c-retinaldehyde–binding protein–positive cells represented Müller cells.[17] The retinal pigment epithelium apparently becomes incorporated into and proliferates within the membrane in the pattern of a nonspecific repair response to tissue injury. Inflammatory cells that expressed leukocyte common antigen were present within five of eight of the membranes (63%) examined. We did not immunostain for specific inflammatory cell subtypes because of the small number of sections obtained from our specimens. These inflammatory cells probably consisted of macrophages, lymphocytes, and plasma cells since these cell types have been demonstrated in surgically excised age-related macular degeneration subretinal neovascular membranes[7] and all three cell types may express leukocyte com-

TABLE 2
IMMUNOHISTOCHEMICAL AND HISTOCHEMICAL FINDINGS IN SUBRETINAL NEOVASCULAR MEMBRANES IN THE SECOND EIGHT PATIENTS WITH AGE-RELATED MACULAR DEGENERATION

PATIENT NO.	FACTOR VIII–RELATED ANTIGEN	C-RETINALDEHYDE–BINDING PROTEIN	MUSCLE-SPECIFIC ACTIN	COLLAGEN TYPE II	COLLAGEN TYPE III	COLLAGEN TYPE V	MUCOPOLY-SACCHARIDE	NEUTRAL LIPID
9	No	Yes	No	No	No	Yes	Yes	Yes
10	Yes	No	Yes	No	Yes	Yes	Yes	Yes
11	Yes	Yes	No	No	Yes	No	Yes	Yes
12	Yes	Yes	No	No	Yes	No	Yes	Yes
13	No	Yes	No	No	Yes	No	Yes	Yes
14	No	No	No	No	Yes	No	Yes	Yes
15	Yes	Yes	No	No	Yes	Yes	Yes	Yes
16	No	Yes	No	No	No	No	Yes	Yes

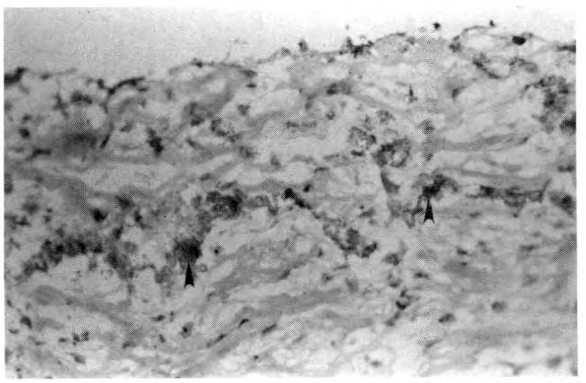


Fig. 9 (Grossniklaus and associates). Patient 12. A bleached section demonstrates positive staining for c-retinaldehyde–binding protein in the monolayer of retinal pigment epithelium (arrowheads) within the membrane (diaminobenzidine, × 40).

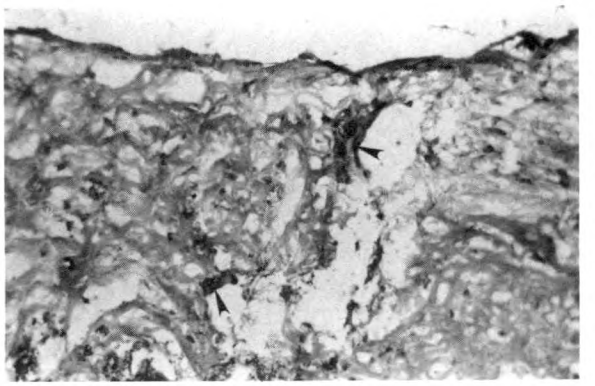


Fig. 10 (Grossniklaus and associates). Patient 12. Cells that stain positive for factor VIII–related antigen (arrowheads) are present within the membrane (diaminobenzidine, × 40).

mon antigen.[18] The inflammatory cells may have been introduced via endothelium-lined vascular channels within the membranes or leached into the membranes from adjacent retina or choroid. The inflammatory component of the membranes appears to be involved as a dynamic component in the formation of the membranes, including release of enzymatic products and remodeling.[7,14] Vascular endothelium had antigenic determinants for factor VIII–related antigen[19] and was found in four of eight of the membranes examined. This corresponds to ultrastructural[7] and immunoelectron microscopic[8] evidence of endothelium-lined vascular channels in previously studied surgically removed subretinal neovascular membranes from patients with age-related macular degeneration. The relatively low percentage of membranes with factor VIII–related antigen–positive cells may be caused by a lack of sensitivity of the antibody or atrophy of vascular endothelium cells within the membranes. The vascular endothelium is considered to be of choroidal origin and enters the subretinal space via a break in Bruch's membrane,[2] although a histopathologically detectable defect in Bruch's membrane is not necessary for subretinal neovascularization.[20] Glial cells and photoreceptors were present in 38% and 13% of the membranes, respectively, with glial cells staining for glial fibrillary acid protein[21,22] and S-100 protein,[21,23] and photoreceptor cells being characterized by staining for neuron-specific enolase.[21,24,25] There was one instance each of S-100 positive/glial fibrillary acid protein–negative cells and vice versa within the same membrane (Patients 3 and 4). This may have been caused by a lack of sensitivity of the immunostains or individual cells being only present in a specific tissue section. The cells that were neuron-spe-

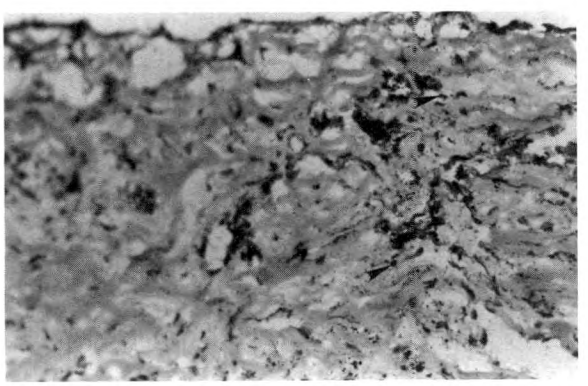


Fig. 11 (Grossniklaus and associates). Patient 12. Droplets of neutral lipid (arrowheads) are scattered throughout the extracellular matrix of the membrane (oil red O, × 40).

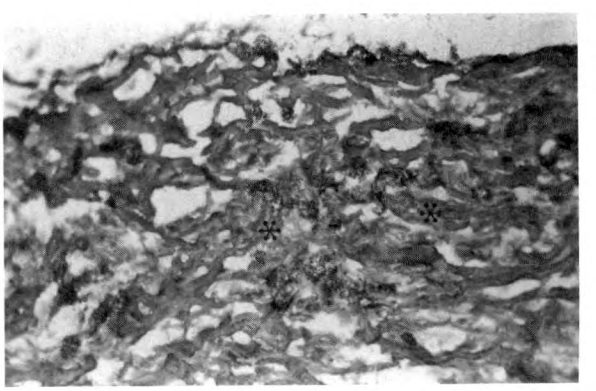


Fig. 12 (Grossniklaus and associates). Patient 12. Type III collagen strongly stains in the extracellular matrix of the membrane (diaminobenzidine, × 40).

cific enolase–positive in one membrane in our study may have represented glial cells that cross-reacted for neuron-specific enolase[26] or other neuronal elements derived from the retina[21,24,25]; however, an internal positive control of photoreceptors in that case plus previous ultrastructural evidence[7] indicates that the neuron-specific enolase–positive cells were probably photoreceptors incorporated into the membrane. Photoreceptor cells have previously been demonstrated by ultrastructural examination to be present in approximately 30% of membranes[7] and it is not surprising that glial cells are also present. Both photoreceptors and glial cells are contributed to the membranes by the neurosensory retina and the expression of glial fibrillary acid protein by the glial cells is consistent with a reactive phenomenon.[21,22] Glial cells occasionally formed monolayers of cells on the membranes. Muscle-specific actin–positive cells were thought to represent myofibroblasts and were present in one of the membranes. This corresponds to ultrastructural evidence of myofibroblasts in 10% of membranes.[7] Some of the muscle-specific actin–positive cells may represent vascular pericytes; however, we believe this is unlikely because the muscle-specific actin–positive cells were not associated with factor VIII–related antigen–positive endothelial cells. Myofibroblasts may develop after transformation of fibrocytes[27] or retinal pigment epithelium. These myofibroblasts may contract and result in further breaks in Bruch's membrane, thus leading to additional subretinal neovascularization.[4] Numerous spindle-shaped cells that were surrounded by collagen in the membranes failed to stain with the antisera tested. These cells were presumed to represent fibrocytes because of their histologic appearance, presence in a collagenous matrix, and previous ultrastructural evidence.[7] These fibrocytes are of probable choroidal origin, although they may also have originated from transformed macrophages.[27]

Immunohistochemical staining disclosed the extracellular matrix to be composed of collagen types I and IV, laminin, and fibronectin in eight of eight of the membranes, collagen type III in six of eight of the membranes (75%), and collagen type V in three of eight of the membranes (38%). Collagen types IV and V are present within the basement membrane of the retinal pigment epithelium and choriocapillaris[10] and collagen type I is present in the inner and outer collagenous zones of Bruch's membrane.[10] Additionally, collagen types I and III are produced during wound repair and granulation tissue proliferation.[15] Type III collagen is produced early in wound repair and mature wounds contain abundant type I collagen. The presence of type I collagen in 100% and type III collagen in 75% of the subretinal neovascular membranes we examined may be related to the age of the membranes, with type III collagen found in less mature membranes. Type V collagen forms anchoring fibrils that attach basement membrane to underlying connective tissue and may be present in granulation tissue proliferation.[28] Laminin is an attachment protein produced by endothelial cells[29] and is found within the basement membrane of the retinal pigment endothelium and choriocapillaris in Bruch's membrane.[10] Laminin is also present in the perivascular region in well-developed capillaries in granulation tissue.[30] Fibronectin is produced by fibroblasts,[15,29] helps cells attach to surrounding structures, is prominent in granulation tissue where it can be associated with actin fibers,[31] and is present in the inner and outer collagenous zones of Bruch's membrane.[10] Fibronectin was also present in the interphotoreceptor cell matrix in membranes in our study, a location normally devoid of fibronectin.[32] Fibronectin is highly concentrated in diffuse drusen.[33] Newsome and associates[33] speculated that high fibronectin concentration in diffuse drusen may in part be responsible for the association of diffuse drusen with subretinal neovascularization.

Histochemical stains were positive for mucopolysaccharide and neutral lipid in all of the membranes. The extracellular mucopolysaccharide stained most intensely with alcian blue at a pH of 1.0, indicating the presence of sulfated mucopolysaccharides.[12] This finding may in part correspond to the presence of heparin sulfate proteoglycan normally present in Bruch's membrane.[10] Neutral lipid was generally scattered throughout the membranes and may have originated from unresorbed serum lipid leached through porous vascular channels in the membranes. Lipid was also present in the cytoplasm of and immediately subjacent to the retinal pigment epithelium, which corresponds to an increased presence of neutral lipids, especially esterified fatty acids, in Bruch's membrane as it ages.[9] Because subretinal neovascularization in age-related macular degeneration is really intra-Bruch's membrane neovascularization with Bruch's membrane containing diffuse drusen, it was not surprising to find the extracellular matrix constituents of the mem-

branes we examined to contain similar material as in Bruch's membrane[10] and drusen.[33]

Subretinal neovascularization in age-related macular degeneration probably represents a nonspecific, localized, stereotypic wound repair response to a stimulus present in age-related macular degeneration. The stimulus is unknown at this time and may be multifactorial. Candidates that may be involved with the formation and growth of subretinal neovascularization include platelet-derived growth factor, transforming growth factor beta, integrins, and plasminogen activators, as these substances have been demonstrated in granulation tissue, periretinal membranes, and elsewhere in the eye.[30,34,35] Reddy and associates[36] recently identified transforming growth factor beta and other growth factors in subretinal neovascular membranes in age-related macular degeneration. We did not examine for these substances because of the small number of sections obtained from our specimens. Further studies are warranted to determine the stimulus for the formation and growth of subretinal neovascularization in age-related macular degeneration.

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Aqueous Dynamics in Exfoliation Syndrome

N. Ziai Gharagozloo, M.D., Robert H. Baker, M.D., and Richard F. Brubaker, M.D.

Eighteen untreated patients with unilateral exfoliation syndrome without glaucoma were studied with regard to differences in aqueous dynamics between the affected and unaffected fellow eyes. Additionally, both eyes of the patients with exfoliation were compared to the eyes of 18 age-matched and gender-matched control subjects. Intraocular pressure was significantly higher (13.9 ± 3.0 mm Hg [mean ± standard deviation]) in the affected compared with the unaffected eyes (12.2 ± 2.5 mm Hg), but no difference in aqueous humor flow was detected when eyes in the three groups were compared (affected eyes, 2.40 ± 0.60 μl/min; unaffected eyes, 2.40 ± 0.65 μl/min; control eyes, 2.61 ± 0.60 μl/min). Anterior chamber volumes were significantly smaller in affected (122 ± 37 μl) and unaffected eyes (121 ± 37 μl) of the patients with exfoliation compared with the eyes of the control subjects (145 ± 30 μl). Apparent resistance was higher in the eyes with exfoliation (6.5 ± 1.9 min mm Hg/μl) compared with both unaffected (5.4 ± 1.2 min mm Hg/μl) and control groups (5.2 ± 1.8 min mm Hg/μl), although these differences were not statistically significant.

EXFOLIATION SYNDROME is usually recognized by a characteristic pattern of white deposits on the anterior capsule of the lens.[1,2] The white fibrillogranular deposits are not limited to the lens capsule, however, and can also be found on the zonular ligaments of the lens,[3] as well as in the iris,[4-6] ciliary body,[4,7] trabecular meshwork,[5,8,9] and conjunctiva.[10] The source of the exfoliative material remains unknown. It is presumed that the increased intraocular pressure in patients with exfoliation syndrome is secondary to increased outflow resistance that results from mechanical blockage of the trabecular meshwork by pigment and exfoliative material.

In a study of ten patients with unilateral exfoliation glaucoma, Johnson and Brubaker[11] found aqueous flow was reduced by 20% in affected eyes compared to unaffected fellow eyes. These patients were all undergoing medical therapy for glaucoma, including treatment with the aqueous suppressing agent, timolol, although the drug was discontinued one week before the study.

Lutjen-Drecoll, Futa, and Tamm[12] observed ultrastructural changes in the ciliary epithelium of eyes with exfoliation glaucoma that indicated increased protein synthesis and decreased active transport in these cells. Such changes were not present in normal eyes of the same age group or in eyes with primary open-angle glaucoma. From these data, one can postulate that the primary site of involvement in exfoliation glaucoma may be the ciliary epithelium, and that either malfunction of or damage to this structure could result in the observed reduction in aqueous formation. This finding also raises the possibility that early aqueous flow suppression may occur in preglaucomatous eyes with exfoliation and mask the early change in outflow resistance. We investigated the aqueous dynamics of eyes with unilateral exfoliation syndrome without a history of glaucoma or treatment for glaucoma.

Material and Methods

Eighteen patients (16 women and two men) with unilateral exfoliation syndrome were included in the study. All patients underwent a complete ocular examination, which consisted of slit-lamp biomicroscopy, applanation tonometry, and dilated fundus examination. Pa-

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Reprint requests to Richard F. Brubaker, M.D., Mayo Clinic, 200 First St. S.W., Rochester, MN 55905.

TABLE
AQUEOUS DYNAMICS DATA*

	AFFECTED EYES				UNAFFECTED EYES				CONTROL EYES			
VARIABLE	NO. OF SUBJECTS	MEAN	SD	SEM	NO. OF SUBJECTS	MEAN	SD	SEM	NO. OF SUBJECTS	MEAN	SD	SEM
Age (yrs)	18	70.4	7.3	1.8	18	70.4	7.3	1.8	18	68.3	3.5	0.8
Refractive error (+ diopters)	17	0.91	1.91	0.48	17	0.71	1.97	0.49	18	0.65	1.88	0.45
Anterior chamber volume (μl)	18	122.3	36.8	8.9	18	120.6	36.5	8.9	18	144.9	29.5	7.2
Intraocular pressure (mm Hg)	17	13.9	3.0	0.7	17	12.2	2.5	0.6	18	12.9	2.7	0.7
Aqueous flow (μl/min)	16	2.40	0.60	0.15	18	2.40	0.65	0.16	18	2.61	0.60	0.15
Apparent resistance (min mm Hg/μl)	15	6.5	1.9	0.5	17	5.4	1.2	0.3	18	5.2	1.8	0.5

*SD indicates standard deviation of the mean; SEM indicates standard error of the mean; NS indicates not statistically significant.

tients with any evidence of exfoliation disease in the fellow eye, ocular hypertension (intraocular pressure > 22 mm Hg), obvious glaucomatous disk damage, or visual field defects were excluded. Patients with a history of laser or intraocular surgical procedures were also excluded from the study. None of the patients was using ocular medications or systemic beta blockers.

A second group of 18 patients who had no evidence of ocular disease (except early cataracts) and who were age-matched (± 10 years) and gender-matched with the study group were recruited to serve as normal control subjects.

On the day of the study, the subjects were instructed to awaken at 2 A.M. and administer one to three drops of 2% fluorescein into each eye and then return to sleep. Fluorophotometry began at 8 A.M. and continued hourly until 4 P.M. The aqueous flow rate was calculated by using the clearance of fluorescein from the anterior chamber after subtracting a diffusional loss factor of 0.25 μl/min from the clearance value.[13] In this manner, hourly aqueous flow rates as well as mean daytime flow (8 A.M. to 4 P.M.) were determined.

The intraocular pressure was measured by applanation tonometry in both eyes of each

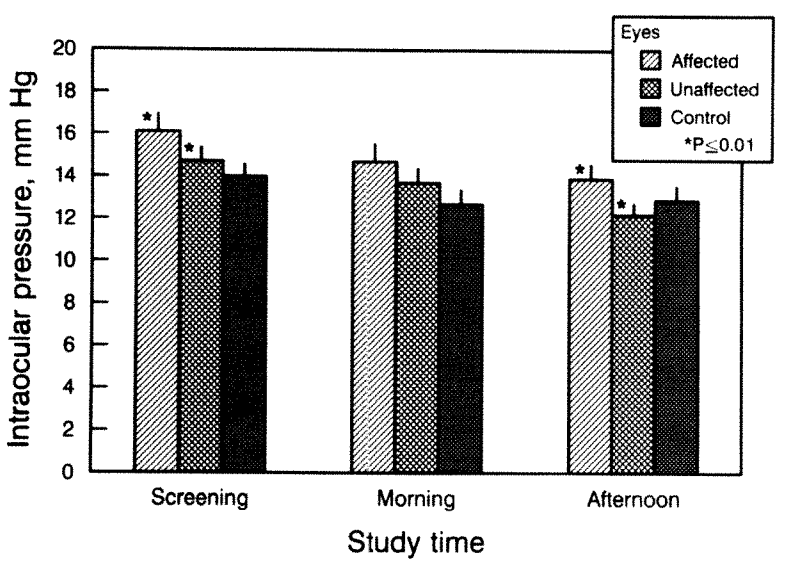


Fig. 1 (Gharagozloo, Baker, and Brubaker). Mean intraocular pressure measurements recorded in patients with exfoliation (affected and unaffected eyes) and control subjects during the screening examination and on the morning (8 A.M.) and afternoon (4 P.M.) of the day of study. Asterisks indicate $P \leq .01$.

TABLE *(Continued)*
AQUEOUS DYNAMICS DATA*

P VALUES		
AFFECTED VS. UNAFFECTED EYES	AFFECTED VS. CONTROL EYES	UNAFFECTED VS. CONTROL EYES
NS	NS	NS
NS	NS	NS
NS	<.05	<.05
<.01	NS	NS
NS	NS	NS
NS	NS	NS

subject at 8 A.M. and 4 P.M. Although tonographic facility of outflow was not measured, the resistance to aqueous outflow was calculated by the ratio of intraocular pressure to aqueous flow. This value, which is not equal to the reciprocal of tonographic facility of outflow, was reported as the apparent resistance. Anterior chamber volumes were measured by a photogrammetric method in all participants.[14]

The patients' eyes were categorized into the following three groups: eyes with exfoliation (affected), the normal fellow eyes of the patients with exfoliation (unaffected), and the normal eyes of the control subjects (control). The data for the control subjects were reported as the mean values for both eyes.

The Student's two-sided *t*-test for paired samples was used to analyze differences between the affected and unaffected eyes of the patients with exfoliation. The Student's *t*-test for independent groups was used to compare the affected and unaffected eyes to the eyes of the control population. For all analyses, a P value of less than .05 was considered statistically significant.

Results

The mean age, refractive error, anterior chamber volume, intraocular pressure, aqueous flow rate, and apparent resistance in the three groups of eyes (affected, unaffected, and control) were analyzed (Table). Although there was no difference in anterior chamber volume between affected and unaffected eyes, anterior chamber volume was significantly smaller in both of these groups of eyes compared with the control group ($P < .05$). No significant differences in refractive error between the three groups of eyes were noted.

As expected, intraocular pressure was significantly higher in the affected eyes compared with their unaffected fellow eyes ($P < .01$), but no significant difference between the intraocular pressure in these eyes and the control eyes was detected (Fig. 1). Apparent resistance was higher in the affected eyes compared with both unaffected and control groups, but these differ-

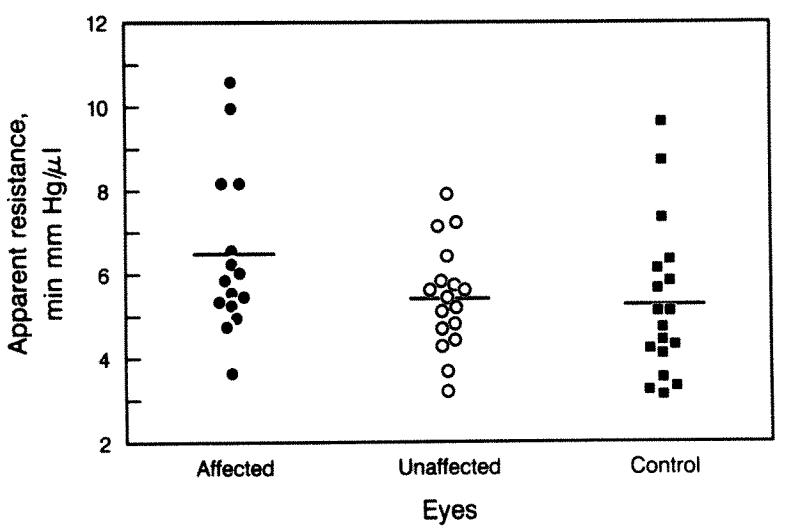


Fig. 2 (Gharagozloo, Baker, and Brubaker). Individual apparent resistance values (intraocular pressure/aqueous flow) in the three groups of eyes (affected and unaffected eyes of patients with exfoliation and eyes of control subjects). Horizontal bars indicate mean values for each group. No statistically significant differences in apparent resistance were found between the three groups.

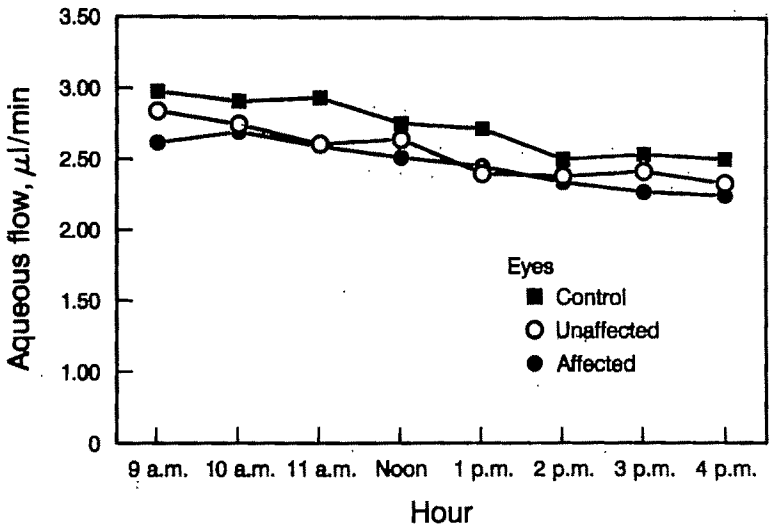


Fig. 3 (Gharagozloo, Baker, and Brubaker). Mean hourly aqueous flow rates in eyes of control subjects (squares) and affected (solid circles) and unaffected (open circles) eyes of patients with exfoliation. No statistically significant differences in flow rates were detected between the three groups.

ences were not statistically significant (Table; Fig. 2).

Hourly aqueous flow was measured in the affected, unaffected, and control eyes (Fig. 3). Mean daytime (8 A.M. to 4 P.M.) aqueous flow in all three groups of eyes was determined (Table). Flow measurements in two subjects in the exfoliation group were excluded because of an excess initial corneal concentration of fluorescein.

This study had a 95% chance of demonstrating a 17% difference in aqueous flow between the affected and unaffected eyes of patients with exfoliation. It had a similar chance of detecting a 30% difference between the affected and unaffected eyes compared with the normal control eyes. However, no significant differences in aqueous flow were detected between the three groups. The relative reduction of aqueous flow in the afternoon, a pattern consistently observed in normal subjects, was present in all three groups (Fig. 4).

Aqueous flow in the affected and unaffected eyes of the patients with exfoliation was also compared to daytime flow values in 304 normal eyes measured by our fluorophotometer over the past decade (Fig. 4). When the measured flow values in the eyes of patients with exfoliation were compared to the predicted values for flow based on patient age and the slope of the regression line, no significant differences were noted, which further suggested that flow in these eyes was within the normal range.

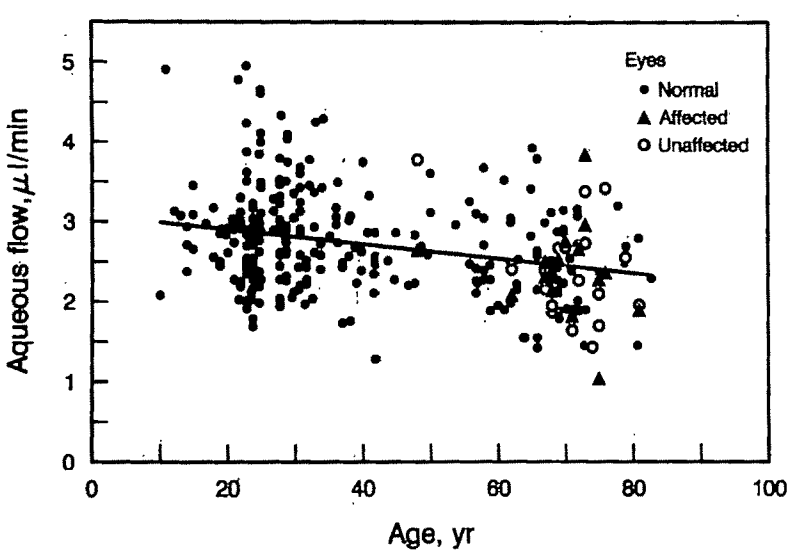


Fig. 4 (Gharagozloo, Baker, and Brubaker). Daytime aqueous flow rates plotted according to subject age in 304 normal subjects (solid circles) compared with flow rates in affected (triangles) and unaffected (open circles) eyes of patients with exfoliation. No statistically significant differences in flow were detected when flow rates in the eyes of patients with exfoliation were compared to predicted flows based on patient age and slope of the regression line.

Discussion

As expected, our results confirmed relatively higher intraocular pressure in eyes with exfoliation syndrome compared with their normal fellow eyes. More importantly, however, we did not demonstrate any significant difference in aqueous flow rate between exfoliative eyes and their age-matched and gender-matched control eyes. Furthermore, a comparison of measured flows in the affected and unaffected eyes of the patients with exfoliation to age-predicted values based on cumulative flow data from our laboratory confirmed that flow in these eyes was within the normal range.

Those results may appear to be in conflict with the previous study of Johnson and Brubaker.[11] However, a simple explanation can resolve the apparent inconsistency. Analysis of the previous study of patients with exfoliation glaucoma discloses that all of the subjects were being treated with timolol, which was discontinued one week before the study.[11] The study demonstrated a 20% decrease in flow in the affected eyes. However, according to a recent analysis of aqueous flow rates after withdrawal of timolol treatment,[15] a 14% reduction in aqueous flow would be expected simply from residual timolol effect at one week. We must therefore conclude that to date, there has been no evidence that aqueous flow rate is abnormal in untreated eyes with exfoliation syndrome with or without glaucoma.

Although not statistically significant, our finding that apparent resistance was higher in eyes affected with exfoliation is in agreement with previous reports that the tonographic facility of aqueous outflow is decreased in exfoliation syndrome.[3,16]

Another interesting finding in our study was that the anterior chamber volume was significantly smaller (122 μl and 121 μl vs 145 μl [17%] in the affected and unaffected eyes compared with the control eyes), although no difference was detected in anterior chamber volume between the affected and unaffected eyes. Furthermore, the smaller anterior chamber volumes in patients with exfoliation could not be attributed to a higher incidence of hyperopia in this population compared to control subjects.

The observation of a smaller anterior chamber in patients with exfoliation is in contradistinction to previous studies that found no difference in anterior chamber volume between eyes with exfoliation and normal control eyes.[17-20] Conversely, Layden and Schaffer[3] found a 23% incidence of narrow angles among their patients with exfoliation compared with an incidence of 5% in the normal population. Several studies of acute angle closure in eyes with exfoliation do exist,[21-24] although by comparison to the total number of eyes with exfoliation, these cases are rare. Nevertheless, it is interesting to speculate as to whether the smaller anterior chamber is a cause of or a result of this disease (that is, an eye with a smaller, crowded anterior chamber could be predisposed to developing exfoliative syndrome or, conversely, a smaller anterior chamber could be a consequence of the syndrome resulting, for instance, from a larger lens).

Our results confirm previous findings that intraocular pressure and apparent resistance are higher in the affected eye of patients with unilateral exfoliation. We detected no difference in aqueous flow between the unaffected eyes of these patients or any difference when these eyes were compared to the eyes of normal control subjects. We question whether the relatively smaller anterior chambers in patients with exfoliation may contribute in some cases to their glaucoma.

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OPHTHALMIC MINIATURE

"That's not exactly what I call pulling over," the patrolman said. "If this was a time of day when there was much traffic you'd be obstructing it. Have your eyes been checked recently?"

For a moment Aurora couldn't quite grasp what he meant: people checked their coats, but why would anyone check their eyes? Then she realized that the redheaded officer had merely spoken imprecisely: he was attempting to inquire about her vision.

"My vision is fine, thank you, Officer," she said. "It's just that I have a little phobia about scraping my tires against the curb. In fact, that's why I was hurrying to my doctor, to see if he could do something about my phobia."

Larry McMurtry, *The Evening Star*
New York, Simon & Schuster, 1992, p. 176

Intraocular Pressure Decrease in Household Contacts of Patients With Hansen's Disease and Endemic Control Subjects

N. Hussein, M.D., T. Chiang, M.D., Q. Ehsan, M.D., and R. Hussain, Ph.D.

We compared the intraocular pressure in 150 urban household contacts of patients with Hansen's disease and 132 endemic control subjects from an urban population in Karachi, Pakistan, who were matched in regard to race, age, gender, and socioeconomic status. The mean intraocular pressure in the upright position was 12.6 mm Hg in the right eye and 12.9 mm Hg in the left eye in household contacts of patients with Hansen's disease and 15.3 mm Hg in the right eye and 15.4 mm Hg in the left eye in the endemic control population ($P < .0005$). The postural change in intraocular pressure from the upright to supine position was 1.7 mm Hg in the right eye and 2.1 mm Hg in the left eye in the household contacts group and 1.3 mm Hg in the right eye and 1.5 mm Hg in the left eye in the endemic control group ($P < .0006$). Our findings, especially in view of past observations in intraocular pressure changes in patients with Hansen's disease, raise serious questions about possible early ocular susceptibility to *Mycobacterium leprae* infection and about public health issues, including possible early indication of disease.

HANSEN'S DISEASE is one of the oldest clinically described diseases of humans. The World Health Organization has estimated that there are 10 to 12 million patients with Hansen's disease, and in many crowded areas of the world, there is more than one case per 1,000 population. This translates into an important public health issue because it is generally assumed that all contacts are at risk in such endemic areas.[1]

Ocular complications are common and perhaps develop more frequently in Hansen's disease than in any other systemic infectious disease. Of the 90% of patients reported to have ocular involvement in some studies,[2] about 7% have a best-corrected visual acuity of worse than 6/60, and 21.3% more have potentially sight-threatening lesions. The ocular complications are limited to the ocular adnexa (eyebrows, eyelids, and nasolacrimal system) and the anterior segment (conjunctiva, cornea, sclera, and anterior uvea).

We have recently drawn attention to findings of significantly low intraocular pressures and significant postural changes in intraocular pressures in patients with Hansen's disease.[3] Furthermore, the intraocular pressure changes occurred both with and without clinical evidence of anterior uveal inflammation and in patients with a mean disease duration of 19.7 years.[4] Concerns have been raised as to the adequacy of treatment in this disease and the criteria for cure from an ophthalmic point of view.[5]

Our studies of Hansen's disease in monkeys suggested that the intraocular pressure changes occurred relatively early (mean duration of 36 months after inoculation with *Mycobacterium leprae* bacilli) and without evidence of anterior uveal inflammation.[6]

In this study, we compared intraocular pressure changes in household contacts of patients with Hansen's disease to those in endemic control subjects in an urban Pakistani population.

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From the Department of Ophthalmology, McGill University, Toronto, Ontario, Canada (Dr. Hussein); the Marie Adelaide Leprosy Center, Karachi, Pakistan (Drs. Chiang and Ehsan); and Department of Microbiology, Aga Khan University, Karachi, Pakistan (Dr. Hussain).

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Reprint requests to N. Hussein, M.D., P.O. Box 809, Stouffville, Ontario, L4A 7Z9, Canada.

Subjects and Methods

We randomly selected 26 urban families that contained index patients with both paucibacillary and multibacillary Hansen's disease. All index patients in these families had a clinical and a bacteriologic diagnosis of Hansen's disease and were on an appropriate multidrug treatment regimen.

We visited the homes of these families by previous arrangement. All members of the household contacts between 15 and 65 years of age and who were living with the index patient were identified and encouraged to undergo a limited ophthalmic examination as our study group. Our endemic control subjects were obtained by contacting subjects from two corporate offices in the city. Both the study group and the endemic control group were matched for race, gender, age, and socioeconomic status (comparable earnings and income scales).

The purpose of the study, the method of ophthalmic examination, and the possible complications were explained to each subject. All who were contacted consented to participate in the study.

We examined the external eye and the anterior segment with a hand-held slit lamp, and the intraocular pressure was measured with applanation tonometry after instillation of topical tetracaine and fluorescein into the inferior fornix.

In each instance, we measured the intraocular pressure with the subject in the upright position and then in the supine position. The pressure in the right eye was always checked first. In a random sample from each group, intraocular pressure measurement was repeated 30 seconds later, with the patient in the upright and supine positions.

The ocular findings were recorded and analyzed separately for each eye. The relationships among variables were established for individual eyes with the Student's *t*-test, analysis of variance, Wilcoxon-Mann-Whitney analysis, and multiple regression analysis. We listed the difference in intraocular pressure in the supine and upright positions as the postural change in intraocular pressure.

Results

One hundred fifty-nine children and adult household contacts lived with the 26 families of patients with Hansen's disease. We included 150 household contacts of patients with Hansen's disease and 132 endemic control subjects in our study. The mean age of the study group and the endemic control group was 35 years and 37 years, respectively.

Of the household contacts, 99 subjects (66%) were contacts of index patients with paucibacillary disease and 51 subjects (34%) were contacts of index patients with multibacillary disease. None of the subjects examined had a history of ocular disease except for optical errors and physical examination of these household contacts did not disclose any clinical signs of Hansen's disease. There was a significant difference in intraocular pressure between the household contacts of patients with Hansen's disease and the endemic control subjects. The intraocular pressure was 12.6 ± 3.2 mm Hg in the right eye and 12.9 ± 3.2 mm Hg in the left eye in the household contacts group and 15.3 ± 3.0 mm Hg in the right eye and 15.4 ± 3.6 mm Hg in the left eye in the endemic control group ($P < .0005$).

There was also a significant difference in the postural change in intraocular pressure between the two groups. Postural intraocular pressure change in the household contacts of patients with Hansen's disease was 1.7 ± 2.0 mm Hg in the right eye and 2.1 ± 2.2 mm Hg in the left eye and the postural intraocular pressure change in the endemic control subjects was 1.3 ± 1.4 mm Hg in the right eye and 1.5 ± 1.7 mm Hg in the left eye ($P < .0006$). The difference in the intraocular pressure between the household contacts of patients with multibacillary Hansen's disease (intraocular pressure of 12.0 ± 3.0 mm Hg in the right eye and 12.7 ± 3.0 mm Hg in the left eye) and household contacts of patients with paucibacillary Hansen's disease (intraocular pressure of 12.9 ± 3.3 mm Hg in the right eye and 12.9 ± 3.4 mm Hg in the left eye) was not significant ($P < .2$).

We found a negative correlation between the intraocular pressure and the postural intraocular pressure change. The relationship for the two variables in the household contacts of the patients with paucibacillary and multibacillary disease disclosed no significant correlation between the intraocular pressure and postural intraocular pressure change in the contacts of patients with paucibacillary disease, but there was a significant negative correlation in household contacts of patients with multibacillary disease (Figure).

No relationship was found between age and

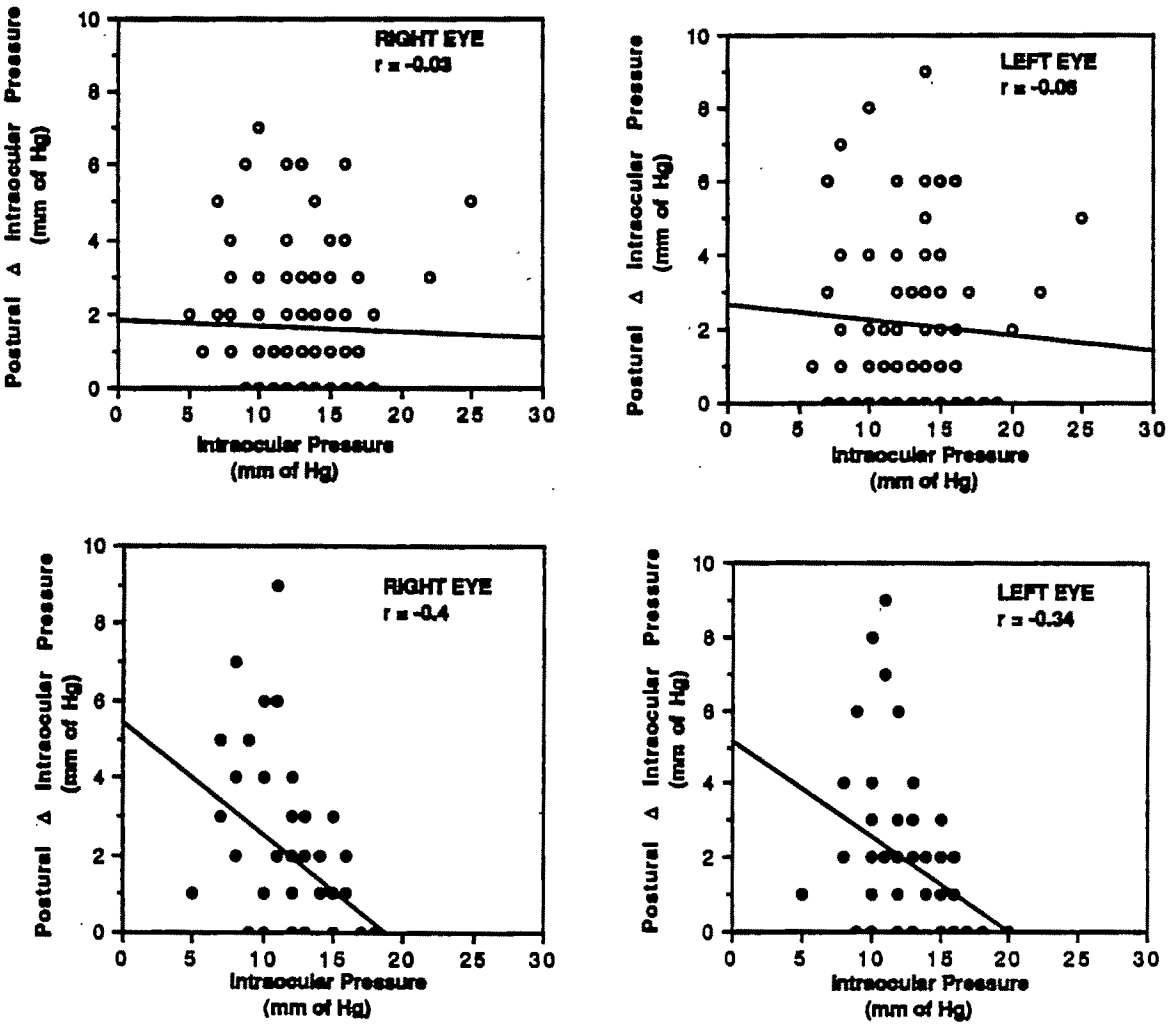


Figure (Hussein and associates). Intraocular pressures and postural change in intraocular pressures in household contacts of patients with paucibacillary disease (top left, right eye and top right, left eye) and multibacillary disease (bottom left, right eye and bottom right, left eye). Note significant negative correlation in household contacts of patients with multibacillary disease.

intraocular pressure in the sample population studied. We divided the household contacts and the endemic control subjects into the following two groups: those younger than 40 years and those 40 years old or older. The mean intraocular pressure in both age groups, between the household contacts and the endemic control subjects, remained significantly different. In the subgroup of subjects younger than 40 years old, the mean intraocular pressure was 12.7 mm Hg in the right eye and 13.0 mm Hg in the left eye and 15.6 mm Hg in the right eye and 15.7 mm Hg in the left eye in the household contacts group and the endemic control group, respectively (Wilcoxon-Mann-Whitney analysis, $P < .001$).

In the subgroup of subjects 40 years old or older, the mean intraocular pressure was 12.2 mm Hg in the right eye and 12.2 mm Hg in the left eye and 15.0 mm Hg in the right eye and 15.1 mm Hg in the left eye in the household contacts group and the endemic control group, respectively (Wilcoxon-Mann-Whitney analysis, $P < .001$).

Intraocular pressure measurements were repeated in 30 members of the household contacts group and 30 members of the endemic control group. There was no difference in the initial and repeat intraocular pressure measurement in the upright position between the groups. In the household contacts, the repeat measurement of postural change in intraocular

pressure was 2.1 ± 2.3 mm Hg in the right eye and 2.4 ± 2.2 mm Hg in the left eye and in the endemic control subjects, it was 1.4 ± 1.7 mm Hg in the right eye and 1.5 ± 1.7 mm Hg in the left eye. This repeat measurement was not significantly different from the initial measurement ($P < .2$).

Discussion

Prevention of blindness and other disabilities in Hansen's disease is the major goal in the care of patients with Hansen's disease after adequate treatment of the infection. The key to prevention of blindness and disabilities is early diagnosis and treatment, the surveillance of high-risk individuals, patient education, and effective treatment of specific complications.[7]

Transmission of Hansen's disease is generally believed to be airborne, with overcrowding, poor hygiene, and immune susceptibility as predisposing factors for infection. Serologic studies suggest that subclinical infection with *M. leprae* is far more common than is generally suspected.[1] We believe that ocular involvement occurs during the early bacteremic phase of infection, which results in bacilli lodging and multiplying in the dopa-rich vascular ciliary body or that ocular involvement occurs through early involvement of the autonomic nervous system and retrograde spread of infection to the eye and ciliary body through the autonomic nervous system. Previous observations and our findings support either pathway of infection and the resulting ciliary body involvement is sufficient to explain the clinical ocular disease spectrum of loss of accommodation, iris atrophy, pinpoint pupils, intraocular pressure changes, and chronic anterior uveitis seen in Hansen's disease.[8,9]

Our findings of low intraocular pressures in household contacts of patients with Hansen's disease as compared to control subjects suggests early autonomic nervous system or early ciliary body involvement, or both, in those household contacts and that a subclinical infection has occurred. Previous observers have found intraocular pressure changes in study populations with a mean duration of disease of more than 30 years; and in the study of Hansen's disease in monkeys,[6] significant intraocular pressure changes occurred within three years of inoculation with *M. leprae*, without clinical signs of anterior uveal tract inflammation. Our data also suggest that these intraocular pressure changes take place independently of the age of the household contact.

We propose therefore that ocular involvement occurs early in Hansen's disease in endemic populations and is manifested as early subclinical ciliary body involvement with low intraocular pressures in individuals susceptible to the bacilli and with no skin lesions.

The finding of similar intraocular pressure changes in household members exposed to either paucibacillary or multibacillary disease suggests that individuals in endemic populations are equally susceptible to the bacilli. The greater postural changes in intraocular pressure in household contacts of patients with multibacillary disease suggest that these subjects were exposed to a larger load of bacilli during infection and may reflect that this group is more susceptible to infection.

The relationship between ocular autonomic nervous system and homeostasis of intraocular pressure is complex.[10] The postural changes in intraocular pressure were immediate and persistent in our group of patients. We believe that these changes are linked to autonomic adrenergic neuropathy, which is considered part of the pathophysiologic characteristics of the disease process.

Our findings suggest early subclinical ciliary body autonomic neuropathy in Hansen's disease, and we believe that intraocular pressure studies may be valuable for epidemiologic studies and for early diagnosis and treatment of the infection. We are currently conducting immunologic studies on these same patients to further substantiate our thesis.

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Ruth Pfau, M.D., Federal Advisor to the National Leprosy Control Board-Pakistan; David Ulmer, M.D., former Dean of Faculty of Health Science, Aga Khan University; and Jamsheed Wania, M.D. (deceased), consultant ophthalmologist, Aga Khan University, Karachi, Pakistan, provided access to patient populations and field support. Mohsin Kamal facilitated access to the corporate populations in Karachi for eye examinations; Ashar Minai performed statistical analysis; and the Department of Microbiology, Aga Khan University, assisted with local logistics.

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OPHTHALMIC MINIATURE

Frank did what he did to all strangers: He walked over to the man, who was obviously in need of a drink, and slapped him on the back. "I'll tell you what, old-timer, if you can tell me which one of these eyes of mine is glass, I'll buy you a drink."

His friends laughed because it was impossible to tell, but the old man looked at him and without a beat said, "The left."

His friends roared, and although Frank was taken aback, he laughed it off as luck and threw a half dollar on the bar.

The bartender watched the party of men leave, and then said to the old man, "What'll it be, mister?"

"Whiskey."

He poured the old man his shot. A little later, the bartender said, "Hey, old friend, how were you able to tell his left eye was glass right off the bat like that?"

The old man drank his whiskey and said, "Easy. The left one was the only one with even a glimmer of human compassion in it."

Fannie Flagg, *Fried Green Tomatoes at the Whistle Stop Cafe*
New York, McGraw-Hill, 1987, pp. 175–176

Asymmetric Pigmentary Glaucoma Resulting From Cataract Formation

Robert Ritch, M.D., Teekhasaenee Chaiwat, M.D., and Thomas S. Harbin, Jr., M.D.

Pigment dispersion syndrome usually manifests bilaterally, and asymmetric involvement is unusual. When asymmetry is present, the eye with greater involvement may have an additional exacerbating condition or the eye with less involvement may be protected. Analysis of such cases should further elucidate the mechanism of the disorder and its development and regression. We examined four patients in whom unilateral cataract formation or extraction was associated with reduced clinical signs of pigment dispersion syndrome in the affected eye. Cataract formation, by inducing relative pupillary block, appears to decrease or prevent the manifestation of pigment liberation.

PIGMENT DISPERSION SYNDROME is characterized clinically by slitlike radial transillumination defects in the midperipheral iris and dispersion of pigment granules on the cornea (Krukenberg spindle), trabecular meshwork, zonules, lens, and anterior iris surface.[1-6] The loss of pigment from the iris results from friction between the posterior iris surface and the zonules during normal physiologic movement.[7] Intraocular pressures may be normal or increased.

Pigment dispersion syndrome appears to be inherited through an autosomal dominant gene.[8,9] Both eyes are usually affected.[1-4] When the severity of phenotypic expression differs between the two eyes, an explanation should be sought. The analysis of asymmetric cases may provide additional information regarding the pathophysiologic mechanism involved or serve as a clue for the existence of additional disease. We examined four patients with unilateral or asymmetric pigmentary glaucoma resulting from unilateral cataract formation or extraction.

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From the Department of Ophthalmology, New York Eye and Ear Infirmary, New York, New York (Drs. Ritch and Chaiwat); and Department of Ophthalmology, Piedmont Hospital, Atlanta, Georgia (Dr. Harbin). This study was supported in part by the Glaucoma Foundation, New York, New York.

Reprint requests to Robert Ritch, M.D., Glaucoma Service, New York Eye and Ear Infirmary, 310 E. 14th St., New York, NY 10003.

Case Reports

Case 1

A 58-year-old white man had had glaucoma diagnosed seven years previously at the time of retinal detachment repair. He had undergone laser treatment for a retinal tear in the right eye after initiation of miotic therapy. He was using 0.5% timolol in both eyes twice daily when first seen. His best-corrected visual acuity was R.E.: 20/20 with −7.00 sphere and L.E.: 20/200 with −10.00 sphere. He had a dense Krukenberg spindle and marked radial, slitlike, midperipheral, iris transillumination defects in the right eye only. Intraocular pressures were 18 mm Hg in the right eye and 15 mm Hg in the left eye. The angles were wide open with moderate pigmentation of the trabecular meshwork in the right eye and light pigmentation in the left eye for 360 degrees. There was early nuclear sclerosis in the right eye and a brunescent cataract in the left eye. The central anterior chamber in the left eye was shallower than that in the right. The cup/disk ratio by contour in the right eye was 0.8, while that in the left eye was 0.3. Goldmann visual fields were normal in both eyes.

Case 2

A 57-year-old white man had a nine-year history of glaucoma in both eyes. He was using a combination of 1% epinephrine and 4% pilocarpine in both eyes four times daily when first seen. A maternal uncle had had glaucoma.

His best-corrected visual acuity was R.E.: 20/25 with −5.00 sphere +1.00 cylinder × 5

and L.E.: 20/200 with −6.25 sphere +2.00 cylinder × 5. A fine Krukenberg spindle, typical transillumination defects, and pigment deposition on the posterior lens surface were present only in the right eye. Intraocular pressures were 42 mm Hg in the right eye and 24 mm Hg in the left eye. The angles were wide open in both eyes with a dense band of pigment on the trabecular meshwork in the right eye, but a light one in the left eye. The lens was clear in the right eye and there was a dense cataract in the left eye. The anterior chamber in the left eye was shallower than that in the right eye. The disk in the right eye was tilted with a cup/disk ratio of 0.6 by color and contour, while that in the left eye, seen only after extracapsular cataract extraction with posterior chamber lens implantation, was 0.3. Visual fields were normal.

Case 3

A 27-year-old white man had undergone intracapsular extraction of a traumatic cataract in the left eye four years previously. His best-corrected visual acuity was R.E.: 20/100 with −12.75 sphere +3.25 cylinder × 35 and L.E.: 20/20 with +4.50 sphere +0.50 cylinder × 105. Intraocular pressures were 26 mm Hg in the right eye and 24 mm Hg in the left eye. A Krukenberg spindle and typical iris transillumination defects were present in the right eye only. Gonioscopy disclosed wide open angles with marked pigmentation of the trabecular meshwork in the right eye. The angle was open in the left eye and had no pigmentation of the trabecular meshwork. The disks and visual fields were normal.

Case 4

A 60-year-old white woman had glaucoma in the right eye. She had undergone intracapsular cataract extraction in the left eye seven years previously. When first seen, she was instilling 0.5% timolol and dipivefrin each twice daily in the right eye.

Her best-corrected visual acuity was R.E.: 20/25 with −4.50 sphere +2.00 cylinder × 25 and L.E.: 20/20 with +12.75 contact lens. Krukenberg spindles were present in both eyes, but were more prominent in the right eye. There was extensive midperipheral, slitlike, radial iris transillumination in the right eye for 360 degrees, but only a slight amount inferiorly in the left eye. Intraocular pressures were 18 mm Hg in the right eye and 14 mm Hg in the left eye. The angles were wide open in both eyes with greater pigmentation of the trabecular meshwork in the right eye. Cup/disk ratios were 0.95 in the right eye and 0.8 in the left eye by color and contour. Visual fields were constricted to 20 degrees in both eyes; additionally, the right eye had a superior hemifield defect with split fixation.

Discussion

Pigment dispersion syndrome can develop with or without increased intraocular pressure. The chance of developing glaucoma in a person with pigment dispersion syndrome is about 50%.[10-12] However, the prevalence of pigment dispersion syndrome has probably been considerably underestimated, and the percentage of affected persons who develop glaucoma is probably much lower.[13]

Pigment dispersion syndrome appears to be an autosomal dominant disorder.[8,9] It most commonly manifests with symmetric involvement in myopic whites, usually between the third and fifth decades. Affected males are more likely to develop glaucoma. A structural abnormality of the iris in relation to the zonules results in mechanical release of pigment caused by rubbing of the posterior iris against the zonular bundles.[7] The loss of pigment and cells overlying the zonules is seen clinically as a midperipheral radial pattern of slitlike iris transillumination defects.

Increased intraocular pressure may be caused, at least initially, by accumulation of pigment in the trabecular meshwork, which blocks aqueous outflow. Patients with pigment dispersion syndrome may develop a shower of pigment in response to dilation[14] or exercise,[15-17] accompanied by a sudden increase in intraocular pressure and a decrease in the facility of outflow.[16] Experimental perfusion of eyes with uveal pigment increases intraocular pressure and resistance to aqueous outflow.[18-21] Melanin granules are found within trabecular endothelial cells and in intertrabecular spaces, accompanied by endothelial degeneration and sclerosis of the trabecular beams and collapse of the intertrabecular spaces.[22]

The time span during which pigment liberation occurs may be limited.[23] Continued growth of the lens with age is accompanied by a decrease in the average size of the pupil.[24] This combination has been hypothesized to induce relative pupillary block, which in turn would decrease the extent of iridozonular contact and

reduce pigment dispersion. Indirect evidence for this has been inferred from improvement in findings or ease of medical control of intraocular pressure in eyes treated long term with miotics[23] or eyes with miosis associated with increased age.[7]

Decrease or elimination of pigment liberation may lead to gradual recovery of trabecular function. Iris transillumination defects may disappear by resurfacing of pigment or pigment-containing cells.[25,26] Decreased corneal and trabecular pigmentation with normalization of intraocular pressure has been noted in eyes that were followed up for several years.[23-25] Older patients may be misdiagnosed as having low-tension glaucoma if iris transillumination defects are not noted.[27] This evidence suggests a trend toward spontaneous reversal and eventual remission of the process in many patients.[27,28]

Understanding the mechanism of causation also provides an insight into prevention. An abnormally deep midperipheral anterior chamber has been regarded as a risk factor for pigment dispersion.[29] Miotics have a dual effect in the treatment of pigmentary glaucoma by inducing a relative pupillary block in addition to increasing aqueous outflow. Miotics can also inhibit exercise-induced pigment release.[17] Lens dislocation, which also eliminates iridozonular contact, has resulted in reversal of pigmentary glaucoma.[30] Cataract extraction should have a similar effect.

Because a structural abnormality is involved, pigment dispersion syndrome is ordinarily a bilateral disease. Unilateral or asymmetric involvement should be explainable by either lack of expression of the phenotype or disappearance of the clinical signs. Asymmetric manifestation is unusual and should serve as a clue for further investigation.

Asymmetry in the degree of contact between the posterior iris surface and the zonules may lead to asymmetry in the clinical signs and symptoms. Kaiser-Kupfer, Kupfer, and McCain[31] described four patients with asymmetric pigment dispersion syndrome and suggested that risk factors other than the mechanical rubbing may have a role in pigment loss, although they found no other causes in their patients.

There are two ways in which such asymmetry may develop. An additional factor may contribute to worsening of the pigment dispersion syndrome in the more involved eye or improvement of the pigment dispersion syndrome in the less involved eye.

One common cause of asymmetry in eyes with pigment dispersion syndrome is the subsequent development of exfoliation syndrome.[32] Exfoliation syndrome is common in older individuals. Glaucoma results from mechanical liberation of iris pigment from the sphincter region with subsequent blockage of the trabecular meshwork. Initial manifestation appears to be more commonly unilateral than bilateral, at least in the United States.

Other causes of miosis can result in asymmetric pigment dispersion syndrome. Krebs and associates[33] described a patient with unilateral Horner's syndrome with more severe involvement of the opposite eye. Asymmetry can also mimic Horner's syndrome.[34] Feibel and Perlmutter[35] described four patients with anisocoria and asymmetric pigment dispersion syndrome, all of whom had a larger pupil in the more involved eye.

In our series, Patients 1 and 2 had less pigment dispersion and less glaucomatous damage in the eyes with cataract formation. These patients might initially have had symmetric involvement, but with the onset of cataract formation, the rate of pigment release became less than the rate of disappearance.

The patient in Case 3 underwent intracapsular cataract extraction at the age of 23 years. No clinical signs of pigment dispersion were present in the aphakic eye. The natural course of pigment dispersion syndrome is still not well understood, and the mean age of onset is unknown. Although it may develop occasionally in teenagers, most patients probably develop it when they are between 20 and 40 years old. In the patient in Case 3, it may have begun after cataract extraction. In the patient in Case 4, the glaucoma was more severe in the normal eye, which suggested arrest or regression of the process in the aphakic eye after cataract extraction.

Our patients provide evidence that cataract formation leads to amelioration of pigment dispersion, most likely through the induction of relative pupillary block. Lens extraction before the development of pigment dispersion aborts the phenotypic expression because of elimination of contact between the lens and zonules. One therapeutic approach to pigmentary glaucoma, beyond increasing aqueous outflow or decreasing aqueous production, would be to find the means of eliminating contact between the iris and zonules. Miotic agents induce relative pupillary block and may inhibit the development of the phenotypic expression of pig-

ment dispersion syndrome. Most recently, D. G. Campbell, M.D. (written communication, Dec. 14, 1991) and Karickhoff[36] have provided evidence that laser iridectomy results in anterior movement of the iris away from the zonules. The development of prophylactic measures to prevent the development of glaucoma in pigment dispersion syndrome will be an important advance in the next few years.

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OPHTHALMIC MINIATURE

Washington, D.C., Oct. 28, 1891.

EDITOR AMERICAN JOURNAL OF OPHTHALMOLOGY: I'm not a doctor, M.D., D.D., or D.D.S., but I'm a newspaper man, which includes all degrees. I come to you with a question. Not long ago I happened into an oculist's office, where he was projecting with cold pig's eyes for cataract. I asked him to let me squeeze out a few, and he did it. I fancy it was a good thing for the pig's comfort that he was dead, but I removed the cataract, just the same. Then the doctor told me how the eye restored itself, and how a glass supplied the place of the lost lens. I asked him why oculists, instead of using a glass, did not slip into the place of the clouded lens removed from the human eye a healthy clear lens from a pig's eye, and he said he did not know, that it had never been tried, as far as he knew. He is yet quite new in the profession, and, of course, his knowledge can not be so extensive as yours. What I want to know from you is, is such an operation possible, with any degree of hope as to ultimate success, and has it ever been tried? If not, why not?

With the hope of enlightenment on this subject in THE JOURNAL,

I am yours, sincerely,

W. J. LAMPTON

Am. J. Ophthalmol. 8:384, 1891

The Edrophonium-Hess Screen Test in the Diagnosis of Ocular Myasthenia Gravis

Gustavo E. Coll, M.D., and Joseph L. Demer, M.D.

The interpretation of the edrophonium (Tensilon) test in the diagnosis of acquired strabismus caused by myasthenia gravis has been problematic because of poorly defined endpoints and unknown sensitivity and specificity. We evaluated the endpoint criteria, dynamics, sensitivity, and specificity of binocular alignment in response to edrophonium by using the Hess screen test in ten normal control subjects, 12 nonmyasthenic patients with acquired strabismus, and in ten patients with acquired strabismus caused by ocular myasthenia gravis. A positive response to the edrophonium-Hess screen test was defined as a 50% or greater reduction in the strabismic deviation at the fixation point associated with maximum deviation within one minute of edrophonium infusion.

All myasthenic patients had a 50% or greater reduction in the initial deviation within one minute of edrophonium infusion. Myasthenic patients had a statistically significant reduction in the average deviation up to 150 seconds after edrophonium infusion ($P < .05$ for all time periods). In contrast, with or without edrophonium infusion, control subjects had a purely horizontal fluctuation in binocular alignment of less than or equal to 2 degrees for the entire four-minute period after edrophonium infusion. None of the 12 nonmyasthenic patients tested positive to the edrophonium-Hess screen test. According to the criterion of positive response as was defined in this study, the test had a high sensitivity and specificity in this sample. These results suggest that clearly defined endpoint criteria make the edrophonium-Hess screen test a sensitive and specific quantitative study for the diagnosis of acquired strabismus caused by myasthenia gravis.

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From the Department of Ophthalmology, Jules Stein Eye Institute (Drs. Coll and Demer), and Department of Neurology (Dr. Demer), University of California at Los Angeles, Los Angeles, California. This study was supported by National Eye Institute grant EY-08313 (Dr. Demer), and a grant from the Karl Kirchgessner Foundation, Los Angeles, California (Dr. Demer). Joseph L. Demer was a 1990–1992 Research to Prevent Blindness William and Mary Greve International Research Scholar.

Reprint requests to Joseph L. Demer, M.D., Jules Stein Eye Institute, UCLA, 100 Stein Plaza, Los Angeles, CA 90024-7002.

MYASTHENIA GRAVIS is an autoimmune disease in which antibodies are produced against the postsynaptic acetylcholine receptors at the neuromuscular junction of skeletal muscles. Myasthenic patients may have an acquired strabismus that may mimic any known paretic, restrictive, or supranuclear ophthalmoplegia.

The diagnosis of myasthenia gravis can be aided by laboratory studies such as the edrophonium test,[1] electromyography,[2] ocular tonography,[3] and the Lancaster red-green test.[4-6]

The Lancaster red-green test is a binocular, subjective, and dissociative test used to quantitate the innervational effort required to maintain fixation at different positions of gaze, and estimate primary and secondary deviations of paralytic strabismus.[7,8] It slightly differs from the Hess screen test in that the distance between subjects and the tangent screen is 100 cm, rather than 50 cm.[9]

We quantitatively evaluated the Hess screen test as a means to monitor binocular alignment in response to edrophonium in the diagnosis of acquired strabismus caused by myasthenia gravis.

Subjects and Methods

Patients with an acquired strabismus who were referred to the Ocular Motility Laboratory at the Jules Stein Eye Institute underwent analysis with the Hess screen test and edrophonium (Tensilon) infusion. Control subjects with normal binocular alignment and motility were recruited and tested after giving written in-

formed consent to a protocol approved by the Human Subject Project Committee at the University of California at Los Angeles.

Patients underwent a complete binocular alignment and motility examination. For Hess screen testing, subjects wore a red lens over one eye and a green lens over the other eye. They were instructed to superimpose a green streak from a hand-held projector on apparent locations of an array of red targets at up to 30 degrees horizontal and vertical eccentricity on a tangent screen 50 cm away. The target location that had the largest binocular deviation was monitored for four minutes after edrophonium infusion. Intravenous access was obtained by using a butterfly catheter (23 or 25 gauge). A single 1-mg test dose of edrophonium was administered intravenously and followed by a 2-ml saline solution flush to guarantee that the dead space of the catheter would not contain edrophonium. If no change in the binocular deviation was observed on the tangent screen 30 seconds after the test dose, an additional 9 mg of edrophonium was administered for 15 seconds. Immediately after the saline solution flush, an electronic stopwatch was activated and patients maintained fixation at a selected target location on the tangent screen for four minutes. A camera that faced the Hess screen recorded all measurements and stopwatch times on videotape. When blepharoptosis was observed before testing, the eyelid position was also recorded on videotape at the conclusion of the test.

The angle of binocular deviation can be read directly in degrees of arc from the calibrated Hess screen. The measurement of the largest binocular deviation on the Hess screen was calculated by using the two-dimensional distance formula $x^2 + y^2 = z^2$ where x represented the horizontal deviation from the fixation target location in degrees, y represented the vertical deviation from the target location in degrees, and z represented the resultant deviation in degrees from the target location.

The absolute change in degrees and the percent of the deviation (observed deviation/initial deviation, multiplied by 100%) were calculated at 15-second intervals during the four-minute test period. A 100% deviation value corresponded to no change in the initial deviation, and a 0% deviation value corresponded to the complete elimination of the initial deviation.

A positive response to edrophonium was defined as a 50% or greater reduction in the binocular deviation within one minute after edrophonium infusion. This strict criterion for a positive response was chosen to avoid the false-positive tests caused by the small degree of normal fluctuation during testing.

The group of patients with myasthenia gravis (five men, five women; mean age, 47 years [range, 28 to 82 years]) had only ocular symptoms. Ocular myasthenia gravis was diagnosed using clinical and laboratory evidence, including anti-acetylcholine receptor antibodies, edrophonium testing, therapeutic trial of pyridostigmine bromide, and thoracic radiography. All patients were referred to a neurologist, who confirmed the diagnosis of ocular myasthenia gravis through clinical examination and review of laboratory testing, such as anti-acetylcholine receptor antibodies and thoracic radiography. One strabismic patient with a positive edrophonium-Hess screen test who responded to a clinical trial of pyridostigmine bromide and had a single-fiber electromyogram diagnostic of myasthenia gravis, later was found to have a tumor within the cavernous sinus.

The group of nonmyasthenic patients with an acquired strabismus (six men, six women; mean age, 56 years [range, 28 to 75 years]) consisted of three patients with esotropia, two patients with superior oblique muscle palsy, three patients with exotropia, three patients with hypertropia, and one patient with hypotropia. None of the patients had clinical or laboratory evidence of myasthenia gravis.

The control group of subjects with normal binocular alignment and motility (eight men, two women; mean age, 30 years [range, 28 to 39 years]) were free of any systemic, neurologic, ocular, or orbital disease. Before and after edrophonium infusion, control subjects maintained fixation on the same target location on the Hess screen for four minutes to determine normal fluctuation and variability.

Results were determined as mean ± 1 standard error of the mean. Student's two-sided t-test was used to compare groups. Differences at the .05 level were considered significant. Sensitivity and specificity were computed according to conventional statistical definitions.[10] The relative operating characteristic of the test was analyzed according to the method of Massof and Emmel.[11]

Results

All patients with acquired strabismus caused by ocular myasthenia gravis had striking reduc-

tion in their binocular deviation with the Hess screen test during the first minute after edrophonium infusion. The initial deviations of the ten myasthenic patients who underwent the Hess screen test ranged from 5 to 37 degrees. All ten myasthenic patients had a 50% or greater reduction in the deviation within one minute after edrophonium infusion (in eight of ten patients at 15 seconds and in ten of ten patients by 45 seconds). A paradoxical increase in the deviation was often exhibited after 60 seconds.

The initial deviation of the 12 nonmyasthenic patients with an acquired strabismus with the Hess screen test ranged from 5 to 28 degrees. In the first minute after edrophonium infusion, nine of the nonmyasthenic patients (75%) had no reduction in the deviation, and three (25%) had a 9% or less reduction in the deviation. None of the 12 nonmyasthenic patients had a 50% or greater reduction in the deviation within one minute after edrophonium administration.

With or without edrophonium administration, control subjects had a purely horizontal fluctuation in binocular alignment less than or equal to 2 degrees for the entire four minutes. The fluctuation in control subjects was not observed during the first 60 seconds, but usually occurred after 90 seconds.

The average percent deviation and the standard error of the mean after edrophonium infusion were plotted against time for myasthenic and nonmyasthenic patients (Fig. 1). The average percent deviation after edrophonium infusion in ten myasthenic patients remained below 50% of the initial value at 15 seconds, below 62% at 90 seconds, and below 72% at 150 seconds. After 150 seconds, the average percent deviation remained at or greater than 100%, the initial deviation. The average percent deviation after edrophonium infusion in the 12 nonmyasthenic patients remained greater than 100% throughout the four minutes. The difference in response to edrophonium infusion between myasthenic and nonmyasthenic patients was statistically significant up to 150 seconds ($P < .05$ for all time periods).

The sensitivity and specificity of the edrophonium-Hess screen test were plotted against the criterion, the greatest percentage reduction in the deviation within one minute after edrophonium infusion (Fig. 2). The sensitivity and specificity curves intersected for reductions between 10% and 50%. According to our criterion of positive response to edrophonium infusion (a 50% or greater reduction in the largest deviation within one minute of edrophonium infusion), the test had a 100% sensitivity and specificity for this sample of patients.

The relative operating characteristic curve is a plot of sensitivity against specificity of a test, for all possible values of criterion. The area under the curve, as applied to this study, was equal to the probability of a correct diagnosis with this test in a two-alternative, forced-choice paradigm.[11] The area under this curve was 1.00, the ideal value.

Discussion

The response measured with the Hess screen test after edrophonium infusion in all ten myas-

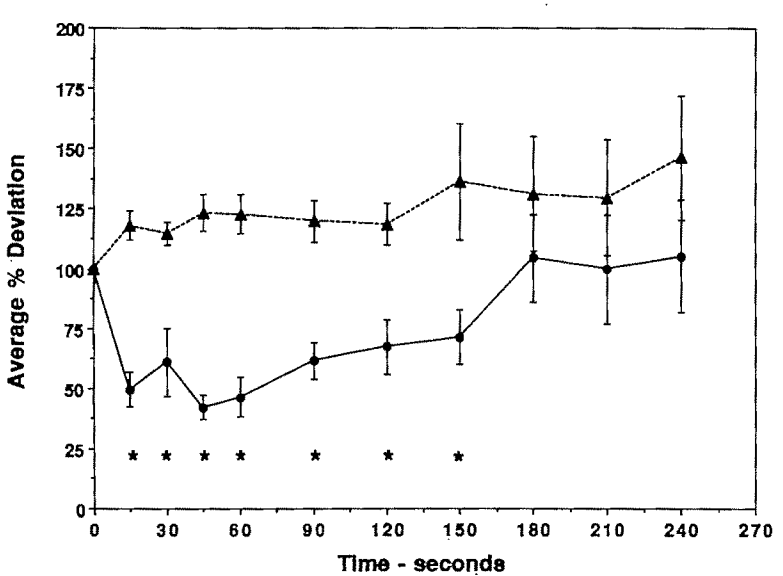


Fig. 1 (Coll and Demer). The average percent deviation and the standard error of the mean after infusion of edrophonium plotted against time for ten myasthenic and 12 nonmyasthenic patients with acquired strabismus. Solid circles and solid lines represent mean values of patients with myasthenia gravis; solid triangles and dotted lines represent mean values of patients with acquired strabismus who do not have myasthenia gravis. Asterisks indicate $P < .05$.

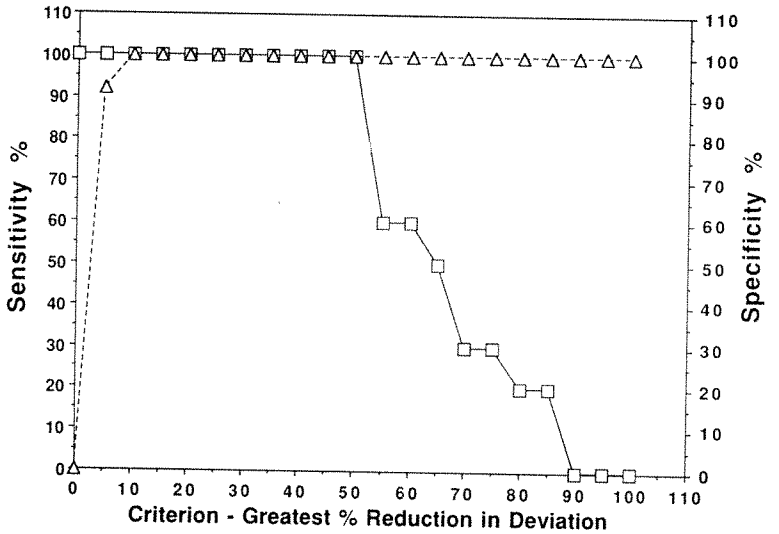


Fig. 2 (Coll and Demer). Sensitivity (solid lines and open squares) and specificity (broken lines and open triangles) of the edrophonium-Hess screen test in the diagnosis of ocular myasthenia gravis plotted against the test criterion, the greatest percentage reduction in the deviation within one minute after infusion of edrophonium. The curves for the sensitivity and specificity intersect between 10% and 50%.

thenic patients with an acquired strabismus was consistent; there was a 50% or greater reduction in the binocular deviation within one minute. Beyond one minute after edrophonium infusion, a paradoxical response was commonly observed in the deviation, which sometimes surpassed the initial deviation. The diagnostic early binocular alignment response to the edrophonium-Hess screen test in strabismic patients can easily be overlooked if measurements are not quickly and accurately obtained during the first minute after edrophonium infusion. Although it is possible to measure the binocular deviation after the infusion of edrophonium by using prisms, it would be difficult to guarantee that the patient maintains prolonged fixation on the same target, or that the examiner can accurately and quickly measure the changes in the primary and secondary deviation with prisms, especially with initial deviations less than 5 degrees. Significant measurement errors with ophthalmic prisms can result if a prism is held in the position for which it is not calibrated,[12] and if the direction of gaze is not strictly controlled when deviations are incomitant. Quickly measuring strabismic deviations with ophthalmic prisms after edrophonium infusion can lead to error in the angular position of the prism and can result in variability in measurements. In contrast, the Hess screen test can easily and accurately measure any changes in binocular deviation as the patient maintains prolonged fixation at a single controlled target location on the tangent screen. In the myasthenic patients with blepharoptosis, the change in the eyelid position after edrophonium infusion lasted longer than the response of the binocular deviation, so eyelid position can also be noted with this test.

Two detailed studies describe the use of edrophonium and the Lancaster red-green test in the diagnosis of myasthenia gravis,[4,5] and there have been additional anecdotal reports.[6,7] Retzlaff and associates[4] administered a complete Lancaster red-green test to myasthenic patients before and at different periods after the infusion of edrophonium.[4] The positive changes in the ocular deviations after edrophonium infusion in myasthenic patients were noted in only some fields of gaze, occurred within the first 20 to 30 seconds, and became maximal at one to two minutes.[4] Glaser[5] described a positive change in only 13 of 15 myasthenic patients after edrophonium infusion, with improvement in some fields of gaze and worsening in others. Both investigators noted a paradoxical response to edrophonium infusion in myasthenic patients.[4,5] These previous studies have lacked specific criteria for the interpretation of the edrophonium test. Our study suggests that the quantitative monitoring of the largest binocular deviation at a single fixation point using the Hess screen avoids the confounding effect of the late paradoxical response to edrophonium infusion, provides a simple method for measuring changes in alignment, and guarantees that, during the critical first minute after edrophonium infusion, changes in the deviation would not be overlooked as might occur if the complete Hess screen test were performed.

With and without edrophonium administration, the fluctuation observed in the control

subjects was 2 degrees or less, was purely horizontal, and usually occurred after 90 seconds from the time of edrophonium infusion. This probably represented the effect of fatigue and accommodative fluctuation. To provide a margin of certainty, we suggest that the horizontal binocular deviation in patients with acquired strabismus be 5 degrees or greater for reliable assessment with the test, because of the normal variability in alignment that can occur. Because no vertical fluctuation was observed in the control subjects with or without edrophonium infusion, any reduction in vertical binocular deviation in patients with an acquired strabismus is marked if it occurs within one minute after edrophonium infusion. These results are similar to those of previous studies that showed that small changes in vertical phorias are more significant than equivalent changes in horizontal phorias.[4,6]

Although the edrophonium-Hess screen test was a simple and safe test to perform in this series, several important technical points were noted during testing. First, it is imperative that the intravenous catheter be adequately flushed with saline solution after infusing edrophonium. This guarantees that no edrophonium remains within the dead space of the catheter and tubing. A second technical point is that within seconds after edrophonium infusion, the red-green goggles often fogged with condensed perspiration released in response to the drug, causing difficulty in seeing the tangent screen red light or the green light from the hand-held projector. Once recognized, this problem was easily remedied by rapidly wiping the subject's goggles with tissue paper and resuming testing.

The curves of the sensitivity and specificity of the predictive functions plotted against the criterion, the largest percent reduction in the deviation within one minute of edrophonium infusion, intersected between 10% and 50%. This intersection suggests that a 30% or 40% reduction in the initial deviation within one minute of the edrophonium-Hess screen test might be an even better criterion to determine a positive response. Although it could not have been known prospectively, the 50% value selected at the start of the study as predictive of a positive response to edrophonium was conservative and accurate. A larger sample would be required to define the optimum criterion more precisely, which might also be influenced by the patient population studied.

It is imperative to obtain measurements of the largest binocular deviation by using the Hess screen test immediately after the infusion of edrophonium. Our study suggests that a positive response to the edrophonium-Hess screen test is invariably exhibited during the first one minute. After the first one minute, a paradoxical increase in the binocular deviation is common. If the initial measurements of the binocular deviation are mistakenly obtained after the first one minute, the test may be incorrectly interpreted as a negative response.

The results of this study suggest that clearly defined endpoint criteria make the edrophonium-Hess screen test a sensitive and specific study for the diagnosis of acquired strabismus caused by myasthenia gravis.

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Behr's Syndrome and 3-Methylglutaconic Aciduria

R. N. Sheffer, M.D., J. Zlotogora, M.D., O. N. Elpeleg, M.D., J. Raz, M.D., and D. Ben-Ezra, M.D.

We examined three patients from two families of Jewish-Iraqi origin who had progressive reduction of visual acuity and childhood onset of bilateral optic nerve atrophy without additional retinal abnormalities. They had neurologic symptoms compatible with Behr's syndrome. Neurologic signs included increased tendon reflexes, a positive Babinski sign, progressive spastic paraplegia, dysarthria, head nodding, and horizontal nystagmus. Neurologic involvement varied between affected siblings. The patients excreted excessive amounts of 3-methylglutaconic acid and 3-methylglutaric acid in their urine. We compared the characteristic ophthalmic features and the spectrum of neurologic signs encountered in this recently delineated autosomal recessive clinical entity with those of previously described entities associated with 3-methylglutaconic aciduria. Patients with early-onset optic atrophy should be examined for neurologic signs and screened for organic aciduria. A detailed ophthalmic examination is important in patients with neurologic abnormalities compatible with Behr's syndrome.

In 1909, Behr[1] described a form of childhood-onset optic atrophy accompanied by neurologic abnormalities. Neurologic involvement included nystagmus, pyramidal and extrapyramidal signs, a positive Babinski sign, increased tendon reflexes, spastic gait, ataxia, and mental retardation. Neurologic signs tended to progress, and then stabilize for many years. Involvement of multiple siblings of both genders, born to healthy consanguineous parents, suggested an autosomal recessive inheritance.[2] Recently, Costeff and associates[3] described a group of patients of Jewish-Iraqi origin who had optic atrophy and variable neurologic involvement compatible with Behr's syndrome. These patients uniformly excreted excessive amounts of the organic acids, 3-methylglutaconic acid and 3-methylglutaric acid, in their urine (Costeff, H., Elpeleg, O. N., Apter, N., Gadoth, N., and Divry, P., unpublished data, 1991).

We examined three new patients from two families with these findings. Awareness of the genetics of the disorder and knowledge of the characteristic ophthalmic findings facilitated rapid and accurate diagnosis of the syndrome.

Material and Methods

Urine samples were obtained from the patients while they were on a regular diet and were stored at −20 C until analysis.

The samples were acidified after the addition of an internal standard (2-phenylbutyric acid), were saturated with sodium chloride, and were subsequently extracted twice by four volumes of ethylacetate. The organic layer was dried over sodium sulfate and evaporated to dryness. The residue was treated with bis-trifluoroacetamide plus 1% trimethylchlorosilane for 30 minutes at 80 C. The trimethylsilyl derivatives were injected into a Hewlett-Packard (Avondale, Pennsylvania) model 5890 series II gas chromatograph equipped with an Ultra-1 cross-linked methyl silicone Gum phase (25 m × 0.2 mm × 0.33 μm) column. Compounds were identified using a Hewlett-Packard 5970 mass-selective detector and quantitations of 3-methylglutaconic acid and 3-methylglutaric acid (C. Jacobs, Ph.D., Free University Hospital, Amsterdam, The Netherlands) were performed in the electron ionization/selective ion monitoring mode while using the authentic 3-methylglutaconic acid and 3-methylglutaric acid for the calibration curve.

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From the Departments of Human Genetics (Drs. Sheffer and Zlotogora) and Ophthalmology (Drs. Raz and Ben-Ezra), Hadassah Hebrew University Medical Center, Jerusalem, Israel; and Metabolic Unit (Dr. Elpeleg), Sha'are-Zedek Medical Center, Jerusalem, Israel.

Reprint requests to Ruth Sheffer, M.D., Department of Human Genetics, Hadassah Hospital, POB 12 000, Jerusalem il-91120, Israel.

Case Reports

Case 1

The patient was the firstborn child of parents of Jewish-Iraqi origin, who were maternal first cousins. She was born after an uncomplicated pregnancy and delivery. Her birth weight was 2,900 g. Psychomotor development was normal. At 1½ years of age, she had febrile convulsions. At that time, horizontal nystagmus was first noted and ophthalmic examination showed decreased visual acuity. At 4 years of age, bilateral optic atrophy was diagnosed. Examination at 4½ years of age disclosed normal physical development. Results of neurologic examination were normal except for head nodding, horizontal nystagmus, and increased tendon reflexes in the lower limbs.

Case 2

The patient was born to paternal first cousins of Jewish-Iraqi origin. She had a similarly affected brother (Case 3), and a healthy brother and sister. Her early psychomotor development was normal. Visual impairment was first noted when she was 8 years old. Examination then disclosed a refractive error of R.E.: $-0.25 -1.25 \times 175$, and L.E.: $-0.50 -1.75 \times 175$, and spectacles were prescribed. At 9 years of age, a further deterioration of visual function was noted. Visual acuity was R.E.: 20/70 and L.E.: 20/100 and temporal pallor of both optic nerves was detected on ophthalmoscopy. The electroretinogram responses were within normal limits. Visual-evoked potential latency was slightly delayed, although its pattern and amplitude were within the normal range in both eyes. A ten-year follow-up of the patient showed that visual acuity has remained unchanged, while pallor of the optic disks has slightly progressed. Electroretinogram responses at 17 years of age were at the lower limit of the normal range. The patient has noticed progressive gait problems since she was 16 years old. She could not walk for long distances and was unable to run. Neurologic examination at 19 years of age showed an unstable spastic gait, increased tendon reflexes in all limbs, a bilateral positive Babinski sign, and pes cavus. Cranial nerves, sensation, and muscle tone were normal.

Case 3

The patient was born prematurely. His birth weight was 1,930 g. Strabismus was noted at 2½ years of age. Ophthalmic examination disclosed temporal pallor of the optic disks in both eyes. Visual-evoked potentials included diminished cerebral responses with an undetectable first positive component, indicative of optic nerve disturbance, and pathologic transfer of impulses from the retina to the occipital cortex. The electroretinogram responses were normal. At 12 years of age, his gait was broad-based, his tendon reflexes were increased, and he had a positive Babinski sign with clonus. Results of computed tomography of the brain were normal. Since then (during the past three years), the patient's neurologic condition has further deteriorated. Recently, he has begun to use a wheelchair and his speech is dysarthric.

Results

Urinary 3-methylglutaconic acid values were 332, 206, and 165 nmol/ml in Cases 1, 2, and 3, respectively. Control values are less than 20 nmol/ml. Urinary excretion of 3-methylglutaconic acid relative to creatinine was 14.8, 14.3, and 14.3 nmol/mol creatinine in the patients, respectively, as compared with control values of 0 to 0.5 nmol/mol creatinine. In the patients' urine samples, values of 3-methylglutaric acid excretion were 79, 41, and 45 nmol/ml, respectively. Control values are less than 20 nmol/ml.

Discussion

In 1989, a familial syndrome of infantile optic atrophy accompanied by a movement disorder, spastic paraplegia, and mild cognitive defects was described by Costeff and associates[8] in ten Israeli Jewish families. Nine of these families were of Jewish-Iraqi origin (originating from Baghdad, Iraq). All affected members excreted large amounts of a specific organic acid, 3-methylglutaconic acid, in their urine. The tenth family from that study was of Ashkenazi Jewish origin. Despite the suggestive clinical features, the affected member did not have organic aciduria. In our three new patients, the clinical features of optic atrophy, together with neurologic symptoms, as well as the origin of the families, suggested that they may also have this syndrome. The detection of large amounts of 3-methylglutaconic and 3-methylglutaric acid in our patients' urine samples confirmed this diagnosis.

The ophthalmic findings of the disease are characteristic. Bilateral optic atrophy with pathologic pallor and attenuation of the papillary vasculature, without other retinal abnormalities, were found in all patients. Visual acuity was decreased. Pathologic red-green discrimination and concentric constriction of the visual fields have also been noted. Additional ophthalmic findings in some of the patients included horizontal nystagmus, strabismus, and gaze apraxia. Visual-evoked potentials showed delayed latencies in most patients, whereas the electroretinogram has remained within normal limits in all patients tested so far. Visual impairment tends to progress during the early stages, remaining unchanged for long periods of time once a visual acuity of 20/70 to 20/100 is attained.

The major neurologic symptoms of the disease were thought to be related to extrapyramidal dysfunction. Many patients have chorea, often severe enough to restrict ambulation. Cerebellar symptoms are common. Spasticity and hyperreflexia, as found in our three patients, are also frequent. The patients are usually of normal intelligence, but some have mild retardation.

The syndrome is variable, especially regarding neurologic manifestations. The degree of neurologic involvement tends to differ between families and may also differ between siblings. Neurologic symptoms can cause severe handicap and some patients are confined to a wheelchair from an early age. In the study by Costeff and associates,[3] symptoms similar to those of Behr's syndrome were noted in patients examined at a neuropediatric rehabilitation center, but it was suggested that the syndrome delineated could be distinguished from Behr's syndrome on clinical grounds because of the marked extrapyramidal dysfunction noted in most of the patients. In our patients, examined at an ophthalmic outpatient clinic, awareness of the ophthalmic pathologic features and the possibility to perform metabolic studies enabled us to detect relatively mild neurologic dysfunction. The patient in Case 2, now 20 years old, does not have extrapyramidal dysfunction and her neurologic signs and symptoms are often encountered in patients with Behr's syndrome. Currently, she leads a normal life, has been able to enroll for military service, and is fully ambulatory. Thus, lack of extrapyramidal signs does not preclude 3-methylglutaconic aciduria. We believe the neurologic courses of our patients and of the patients in the series of Costeff and associates[3] are both compatible with Behr's syndrome, given clinical heterogeneity.

Previously, 3-methylglutaconic aciduria had been associated with three different clinical entities.[4] The first entity was described with 3-methylglutaconyl-CoA hydratase deficiency and characterized by delayed speech development. The second entity was seen in males with cardiomyopathy, neutropenia, and growth retardation. In the third entity, neurologic deterioration and ophthalmic involvement, including optic nerve atrophy, were seen.[5-8] However, in contrast with our patients, most patients had inadequate weight gain and severe neurologic symptoms that began during their first year of life. Neurologic problems include severe developmental delay, loss of previously acquired developmental milestones, spasticity and hypertonia, dyskinetic movements, and convulsions. Additionally, these patients may excrete excessive amounts of other organic acids, including Krebs cycle intermediates. The primary enzymatic defect in the second and third entities is as yet unknown.

The Jewish-Iraqi patients with Behr's syndrome are clinically different from the patients in the first two of the three entities associated with 3-methylglutaconic aciduria. The late onset and relatively mild neurologic clinical course, as well as the lack of additional metabolic abnormalities, also distinguish our patients from the patients with the third entity. Therefore, assignment of a new distinct entity is warranted.[9]

The pathogenesis of optic nerve damage in Behr's syndrome with 3-methylglutaconic aciduria is as yet unclear and study of the underlying enzymatic defect is underway. Existence of clinical entities associated with 3-methylglutaconic aciduria, but unassociated with optic nerve involvement, is noteworthy.

Up to now, Behr's syndrome and 3-methylglutaconic aciduria have been detected in 37 patients from 24 families (O. N. Elpeleg, M.D., unpublished data, 1992), all of whom were Iraqi Jews from Baghdad, and most of whom were born of consanguineous parents. All affected persons from this community are probably descendants of a common ancestor and are probably homozygous for a single mutation (so-called founder effect [a recessive mutation occurring in the founder is passed from generation to generation and, in a society in which consanguineous marriage is prevalent, results in numerous descendants who have inherited the mutation from both parents]). The presence

of the same clinical syndrome without organic aciduria in one of the patients described by Costeff and associates[3] is in accordance with the assumption that Behr's syndrome is heterogeneous, may be caused by different etiologic factors, and is possibly associated with additional inherited metabolic defects. The possibility of mitochondrial DNA defects, as have been found in Leber's optic atrophy, is unlikely, since such defects are maternally inherited.

A thorough neurologic examination and long-term follow-up of patients with early-onset optic atrophy are important. Conversely, children who have compatible neurologic symptoms or familial cerebral palsy should be carefully examined to exclude optic nerve disease. Urinalysis for organic acids should be incorporated as a diagnostic investigation in patients belonging to both categories. Whether Behr's syndrome is associated with 3-methylglutaconic aciduria in non-Jewish or non–Iraqi-Jewish patients requires further study.

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PERSPECTIVES

Neuro-ophthalmic Associations and Complications of Diabetes Mellitus

Ronald M. Burde, M.D.

Neuro-ophthalmic dysfunction in patients with diabetes mellitus is presumed to be caused by metabolic derangement related to activation of aldose reductase and the polyol pathway. This metabolic perturbation causes many consequences, that is, biochemical, structural, and physiologic alterations, some or all of which alter neurologic function.[1] Neuro-ophthalmic dysfunction may also be associated with diabetes mellitus without an obvious causal relationship.

Neuro-ophthalmic Associations of Diabetes Mellitus

Children born to women with diabetes mellitus have an increased incidence of optic disk hypoplasia. The association of optic nerve hypoplasia in a child with a diabetic mother was first noted by Petersen and Walton,[2] and then elaborated by Nelson, Lessell, and Sadun.[3] These authors pointed out that children of diabetic mothers are at risk to have multiple congenital anomalies. In these patients, the optic disk hypoplasia appears to be an isolated defect. Interestingly, patients with optic disk hypoplasia not associated with diabetes mellitus can have a variety of congenital anomalies, including ocular, neurologic, and endocrinologic defects.[2-4]

The findings of optic disk hypoplasia can vary from the easily recognizable extreme (that is, small optic disk, no central cup, and a double ring sign) to subtle changes (normal optic disk size, but thinning of the peripapillary nerve fiber bundles).[4-7] Prevalence data on optic disk hypoplasia are lacking, but affected patients tend to be women (2:1). The optic disk hypoplasia may be unilateral or bilateral (1:1). Most of these patients are visually asymptomatic and have good visual acuity, inferior altitudinal visual field defects, and small optic nerve heads on routine eye examinations. No causal relationship to the diabetes has been established.

The association of juvenile diabetes mellitus and progressive optic atrophy is well known.[8,9] In 1977, Lessell and Rosman[8] emphasized that hearing loss and diabetes insipidus are commonly seen in such patients, but pointed out that these patients could be anosmic as well. The quartet of diabetes insipidus, diabetes mellitus, optic atrophy, and deafness is referred to as Wolfram's syndrome,[9-11] and bears the acronym DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness[12,13]). These patients become increasingly more handicapped because of progressive vision and hearing loss. Generally, diabetes mellitus and optic atrophy tend to develop before the other associated defects. This disorder seems to have a mendelian inheritance pattern of an autosomal recessive disorder.[13,14]

Chronic open-angle glaucoma is best described as a progressive optic neuropathy, the course of which is variably affected by intraocular pressure. Several studies[15,16] have shown a higher prevalence of open-angle glaucoma in patients with diabetes mellitus and vice versa. Similarly, larger cup/disk ratios are also more common in patients with diabetes mellitus. Thus, if one wants to find individuals with chronic open-angle glaucoma, screen patients in a clinic for diabetic patients, and if one wants to find people with diabetes mellitus, screen patients in a clinic for patients with glaucoma.[17(p.280)] Patients with diabetes mellitus tend to lose visual field at lower-than-expected intraocular pressure. Additionally, Zeiter, Shin, and Baek[18] have suggested that diabetic patients with open-angle glaucoma are more likely to develop inferior visual field loss, as opposed to the superior visual field loss ordinarily seen in nondiabetic glaucomatous patients.

Becker[16] found that patients with diabetes mellitus tend to have higher levels of intraocular pressure after the use of topical corticosteroids. Patients with chronic open-angle glaucoma are less likely to develop proliferative diabetic retinopathy. The reason for this relationship remains obscure.

Neuro-ophthalmic Complications of Diabetes Mellitus

A variety of afferent visual system disorders are presumed to be consequences of diabetes.

Anterior ischemic optic neuropathy of the nonarteritic variety is characterized[19-24] by an acute loss of vision (central visual acuity) and visual field loss (usually inferior altitudinal), or both, associated with pallid optic disk swelling (usually superiorly) and flame-shaped hemorrhages within the substance of the optic disk or in the peripapillary retina. A similar episode in the fellow eye can be expected in about 40% of patients and a second episode in the same eye can be expected in 2% to 4%[24] of patients. Most of these patients will have the "disk at risk"[25] as originally pointed out by W. F. Hoyt, M.D. (oral communication, February 1982); that is, a small optic disk, with no central cup, and anomalous branching patterns of the vessels within the optic disk.[26-28] An increased occurrence of diabetes mellitus (20%) has been noted in patients with anterior ischemic optic neuropathy of the nonarteritic variety.[20,23,24]

Guyer and associates[20] found a significantly higher prevalence of diabetes mellitus in patients with anterior ischemic optic neuropathy when compared to a matched population. The prevalence of diabetes was much greater in patients younger than 44 years, 50% of whom had diabetes mellitus. Beri and associates[29] found that male patients with diabetes mellitus who had nonarteritic ischemic optic neuropathy in one eye have a greater risk of involvement in the second eye (1.56 to 2.56 times greater incidence of secondary involvement than patients without diabetes mellitus).[29]

In 1971, Lubow and Makley[30] described three patients with juvenile insulin-dependent diabetes mellitus who had optic disk swelling that was interpreted by some as papilledema. Subsequent studies[31-34] characterized the syndrome as follows: optic disk swelling, often with dilation of the radial peripapillary capillaries in patients with juvenile insulin-dependent diabetes mellitus of some chronicity (greater than five years); unilateral or bilateral, symptomatic, or asymptomatic. Much like the optic disk swelling of anterior ischemic optic neuropathy, the swelling tends to be segmental. With the resolution of the optic disk swelling, the optic disk may appear normal, or there may be diffuse or segmental atrophy. Some of these patients may be symptomatic and experience transient obscurations of vision or visual loss whereas others are asymptomatic and have optic disk swelling noted on routine ophthalmic or medical examination. Because it is impossible to determine the number of diabetic patients who are both asymptomatic and have optic disk swelling, it is impossible to determine the true incidence of this finding. Sequelae may include decreased central visual acuity, or residual visual field defects, usually arcuate. But, in general, visual dysfunction in these patients is secondary to diabetic retinopathy. The visual deficit in these patients usually returns to normal within months to a year. Visual improvement precedes disappearance of the optic disk swelling, usually by months.

Similar to anterior ischemic optic neuropathy of the nonarteritic variety, the papillopathy of diabetes mellitus also occurs in patients with the "disk at risk."[25] It is hypothesized that this condition is a forme fruste of nonarteritic anterior ischemic optic neuropathy.[34] A dilated radial peripapillary capillary net in these patients suggests the presence of a compensatory mechanism that allows the optic disk to survive a postulated chronic low-grade ischemia.

Schwartz[35] described decreased corneal sensation in patients with diabetes mellitus. Chronic open-angle glaucoma, as mentioned previously, is more prevalent in the diabetic population. Topical beta-adrenergic antagonists, which are now considered the first-choice drugs in the treatment of most glaucomas, may have some intrinsic anesthetic properties.[17(p.463)] The use of beta-adrenergic antagonists in such individuals may produce an unstable corneal epithelium that can break down trophically or be abraded by contact-lens wear. With their increased propensity to develop infection, diabetic patients are at risk to develop an infectious keratitis that can lead to disastrous visual loss.

Patients with diabetes mellitus are at risk to develop cranial mononeuropathies, particularly of the oculomotor, trochlear, abducent, and facial nerves. Historically, although most often discussed in the context of occurring almost exclusively in diabetic patients, such palsies, more often than not, occur in patients without abnormalities of glucose metabolism and the more general term vasculopathic mononeuropathy is better applied.[36]

Vasculopathic, including diabetic, monocranial palsies involving the oculomotor nerve are characterized by the finding of pupillary sparing,[37,38] that is, a relatively normal pupillary reaction in face of an almost total somatic palsy. Pupillary sparing is found initially in about 8% to 15% of patients with aneurysms, but the pupil will usually become involved in such patients in three to five days.[39] Pupillary involvement is found in 10% to 20% of patients with vasculopathic palsies.

New evidence suggests that the hypothesis

that cranial mononeuropathies are caused by infarcts of the peripheral nerve[40] is probably not correct. Evolving evidence suggests that many of these mononeuropathies are caused by fascicular disruption within the brainstem secondary to microinfarction.[41] Almost universally, these patients recover completely over a period of two to six months without developing aberrant regeneration.

Bell's palsy (facial nerve cranial palsy) may precede a diabetic ophthalmoplegia in about one third of cases by several months to years.[42] The finding of an isolated Bell's palsy or recurrent Bell's palsy, especially in a young adult, requires an examination for systemic diseases, including diabetes mellitus.

In patients with diabetes of long duration, the pupils tend to mimic those of patients with midbrain disease; that is, they are 4 mm to 5 mm in diameter, round and regular, with decreased pupillary reaction to light and a relatively normal near reaction. Many people believe that these findings are caused by midbrain vascular disease. Conversely, Sigsbee and associates[43] have shown that 75% of patients with diabetes mellitus of some chronicity show cholinergic supersensitivity of the iris, suggesting that the light-near dissociation is attributable to a peripheral autonomic neuropathy.

Similar findings used to be found in patients who had panretinal photocoagulation, more likely because of heating of the short ciliary nerves in the suprachoroidal space than because of the destructive effects of the laser on the iris sphincter itself. On slit-lamp examination, these patients have an Adie's-like pupil with sectoral dysfunction.

Patients with diabetes mellitus are known to develop infectious processes including orbital cellulitis. Orbital cellulitis is characterized by proptosis, periorbital swelling, and ophthalmoplegias.[36(p.288),44] Such patients are almost always febrile and have an increased white blood cell count. Most patients will have concomitant sinus disease. Although generally, the most common infective organisms are bacterial, in any diabetic or immunologically compromised patient, zygomycosis (or other fungal infections) must be the leading diagnosis until excluded by biopsy. The nasopharynx is usually inoculated with spores that develop into nonseptate hyphae. The nonseptate hyphae cause an obliterative arteritis that produces necrotic lesions in the orbit and nasal cavity.

If zygomycosis is suspected, a nasopharyngeal examination must be performed to detect the typical eschar. Although originally thought to occur only in patients with ketoacidosis, it is now known that all diabetic patients are at risk to develop this complication. Treatment consists of wide local debridement and the use of systemic amphotericin B.

A unifying cause must be sought for the associations described in this overview. It would be my best guess, at the present time, that the most insightful investigations will examine metabolic perturbations—either occurring at a critical time in embryogenesis or as a consequence of the accumulation of toxic products.

From the Department of Ophthalmology, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York. This study was supported in part by an unrestricted departmental grant from Research to Prevent Blindness, Inc., New York, New York. This study was presented in part at the Annual Meeting of the American Academy of Ophthalmology, Anaheim, California, Oct. 16, 1991.

Reprint requests to Ronald M. Burde, M.D., Department of Ophthalmology, Albert Einstein College of Medicine and Montefiore Medical Center, 111 E. 210th St., Bronx, NY 10467.

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LETTERS TO THE JOURNAL

Use of the Potential Acuity Meter in Suspected Functional Visual Loss

Leah Levi, M.B.B.S, and Robert M. Feldman, M.D.

Neuro-ophthalmology Unit, Department of Ophthalmology, University of California, San Diego.

Inquiries to Leah Levi, M.B.B.S., UCSD Department of Ophthalmology, Shiley Eye Center 0946, La Jolla, CA 92093-0946.

Patients suspected of having functional visual loss present a creative challenge to the neuro-ophthalmologist, which often leads to using old tools in new ways. The Potential Acuity Meter[1] (Mentor, Norwell, Massachusetts) is an instrument available to most ophthalmologists, and we have found it to be useful in the demonstration of functional visual loss.

During a complete neuro-ophthalmologic examination, inconsistencies in the patient's performance compared to claimed visual dysfunction are noted.[2] While the pupils are dilating, the patient is told a test will be performed that is designed to circumvent the eye problem, and allow us to evaluate what the vision might have been had the injury (or other problem) not occurred.

Once the patient's pupils are dilated, another staff member performs the Potential Acuity Meter test in our absence. The tester gives the patient an explanatory introduction, using wording similar to that of the original explanation. By that time many patients with functional visual loss seem to have decided that the best strategy might be for their "potential" vision to be dramatically better than their claimed visual acuity. If there is functional visual loss, the patient usually demonstrates either normal visual acuity or a visual acuity much better than that claimed by routine Snellen testing. In most cases the visual acuity is better than that obtained by other methods used earlier in the examination.

The Potential Acuity Meter test, together with other findings such as normal visual behavior, normal stereoacuity, nonphysiologic visual field loss, appreciation of entopic phenomena, a positive prism dissociation test,[3] and normal results of a pupillary and fundus examination helps us confirm functional visual loss. This technique also allows us to quantify visual acuity directly. Since using this method we have only rarely needed to resort to visual-evoked potentials to quantify visual acuity.[4]

Grignolo, Moscone, and Boles-Carenini[5] reported the use of Lotmar's Visometer to obtain grating acuity in malingerers. The advantage of the Potential Acuity Meter is its greater availability to most ophthalmologists, and its direct quantitation of the more familiar Snellen acuity. We have found the potential acuity test to be equally useful in adults and children with functional visual loss, particularly when other testing has not succeeded in significantly improving claimed visual acuity.

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Letters must be typewritten, double-spaced, on 8 1/2 x 11-inch bond paper with 1 1/2-inch margins on all four sides. (See Instructions to Authors.) An original and **two** copies of the typescript and figures must be sent. The letters should not exceed 500 words of text. A maximum of two black-and-white figures may be used; they should be cropped or reducible to a width of 3 inches (one column). Color figures cannot be used. References should be limited to five.

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Fig. 1 (Gupta and Basti). Scleral ulceration (8 × 8 mm) and corneal infiltrate (4 × 4 mm) of the left eye.

Corneoscleral, Ciliary Body, and Vitreoretinal Toxicity After Excessive Instillation of Mitomycin C

Satish Gupta, M.D., and Surendra Basti, D.N.B.

Cornea Service, L. V. Prasad Eye Institute.

Inquiries to Satish Gupta, M.D., L. V. Prasad Eye Institute, Road No. 2, Banjara Hills, Hyderabad-500 034, India.

Postoperative instillation of mitomycin C after pterygium excision has been found to reduce the pterygium recurrence rate.[1,2] Administration of 0.02% mitomycin twice a day for five days has been found to be safe.[2] Excessive use of mitomycin may, however, produce complications. We treated a patient who developed ocular complications after taking mitomycin C every eight hours for three weeks.

A 36-year-old woman had a history of redness, pain, watering, and decreased vision in her left eye after instillation of 0.02% mitomycin C every eight hours for three weeks after primary pterygium excision. She had been treated with topical 0.3% ciprofloxacin every three hours, 0.1% dexamethasone every 12 hours, 1% atropine every six hours, and oral dexamethasone, 2 mg every eight hours for one week, but had no relief.

On examination, visual acuity in the patient's left eye was 20/80, improving with pinhole to 20/40. There was conjunctival injection and discharge. Scleral thinning (8 × 8 mm) with necrotic tissue at its base was seen at the site of the pterygium excision (Fig. 1). The adjacent cornea showed a dense, yellow, deep stromal infiltrate (4 × 4 mm) with mild epithelial and stromal edema surrounding it. Keratic precipitates were seen on the endothelium. The anterior chamber showed moderate reaction. The pupil was 4 mm and peaked nasally. The intraocular pressure was 4 mm Hg. Results of the Seidel test were negative. Scrapings for bacterial and fungal cultures were taken from the edges of the ulcer and from the corneoscleral limbus.

Topical fortified gentamicin (13 mg/ml) and cefazolin (50 mg/ml), hourly, and atropine (1 mg/ml), every eight hours, were started. A hypopyon appeared on day 2. Scrapings were repeated but were not contributory. Over the next five days, the anterior segment remained the same. Ophthalmoscopy disclosed vitreous exudates in the inferior periphery. No other details were apparent. Topical pimafuscin (5%) was added hourly. On day 8, vascularization was seen at the edges of the scleral ulcer and within the corneal infiltrate. Thereafter, the hypopyon progressively disappeared, and the area of scleral thinning and the infiltrate decreased. Nine weeks later, topical betamethasone, 0.1% every 12 hours, was added and the pimafuscin was stopped. The infiltrate reduced rapidly with this treatment. The intraocular pressure, however, remained at 6 mm Hg and vision did not improve. Ophthalmoscopy showed moderate vitreous haze and cells, and fluffy vitreous opacities inferiorly. The disk was hyperemic with blurred margins and there was edema at the macula and peripapillary retina. Prednisolone, 40 mg/day, was added orally.

One week later, intraocular pressure was 12 mm Hg, and the vitreous haze had considerably decreased. After a regimen of systemic cortico-

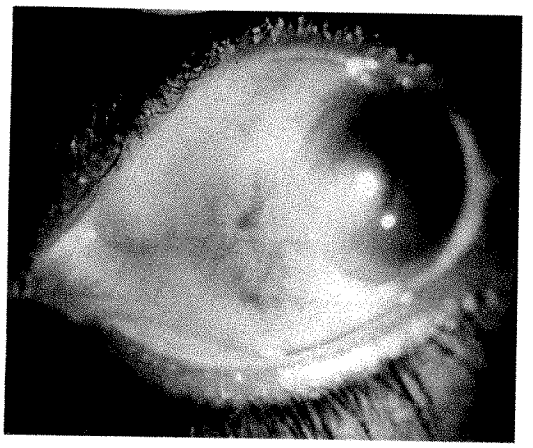


Fig. 2 (Gupta and Basti). Healed scleral defect and resolved corneal infiltrate.

steroids continuously for a month, the disk margins became more distinct, and the macular edema progressively decreased. When the patient was last seen, her visual acuity in the left eye was 20/70, improving to 20/30 with pinhole. The eye was not inflamed, the scleral and corneal lesions had healed (Fig. 2), and intraocular pressure was 10 mm Hg. Ophthalmoscopy disclosed clear vitreous, a normal-appearing disk and macula, and trace edema over the superior and inferior peripapillary retina.

We started anti-infective agents under the presumptive diagnosis of an infective cause. Retrospectively, lack of response to this treatment and failure to isolate any organisms prompted us to consider a toxic origin. This contention was supported by rapid improvement after instillation of corticosteroids. The corneal haze precluded accurate assessment of the fundus. Clearing of the haze permitted diagnosis of the fundus findings. We postulated that the area of extreme scleral thinning caused by mitomycin was the portal through which mitomycin entered the vitreous cavity. Its toxicity on the ciliary body, vitreous, and retina probably caused the hypotony, vitreitis, macular edema, and disk changes.

Although anterior segment complications have been seen clinically after mitomycin C therapy,[1-3] its ciliary body and vitreoretinal toxicity has been described in studies on rabbits.[4,5] Considering the disastrous consequences that can ensue with misuse, application of mitomycin intraoperatively at the site of pterygium excision appears to be safer than its postoperative use.

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Pure Ocular Blast Injury

Itzchak Beiran, M.D., and Benjamin Miller, M.D.

Department of Ophthalmology, Rambam Medical Center (I.B., B.M.) and the Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology (B.M.).

Inquiries to Benjamin Miller, M.D., Department of Ophthalmology, Rambam Medical Center, P.O.B. 9602, 31096 Haifa, Israel.

The term "blast injury" refers to damage caused to body organs by a shock wave originating in an explosion and propagating in a given medium. When the shock wave moves between body spaces, it produces spalling in the interphases inside the body, which causes the expulsion of blood through the capillary wall. Explosion damage is dependent upon distance: wave intensity is decreased to a third power of the distance from its source.[1]

A 20-year-old healthy man was admitted to our department after being exposed to an explosive powder explosion, estimated at 500 kg, from a distance of about 90 m. The patient remained fully conscious and on his feet throughout the explosion event. Three persons standing near him suffered blast injury to their ears and could testify that there was clearly no additional traumatic impact on the patient's

eye. On admission (half an hour after exposure), the patient complained of mild blurring of vision in his left eye. Visual acuity was R.E.: 20/20 and L.E.: 20/30. The right eye was normal. The left eye had conjunctival and ciliary injection. Intraocular pressure was 10 mm Hg. The cornea was clear, with Descemet's folds. The anterior chamber was of normal depth, with a hyphema 3 mm high and multiple floating erythrocytes. The pupil was round, regular, and reactive to light. The lens was in place and clear. The fundus was normal.

Results of computed tomography of both orbits and the brain were normal. During hospitalization, when the patient got up for slit-lamp examination, three events of rebleeding occurred from a vessel at the root of the iris, located at the 11 o'clock meridian. After eight days of strict bed rest, no rebleeding was observed. The patient was discharged after 18 days' hospitalization. The only medications were locally applied corticosteroids administered during hospitalization and thereafter.

At discharge from the hospital, visual acuity in the patient's left eye was 20/20. Intraocular pressure was 16 mm Hg. A blood clot was observed temporally on the iris, the pupil was nearly round, and pigment particles were seen on the anterior surface of the lens. Results of the remainder of the examination were normal.

During a three-month follow-up, the blood clot disappeared, and angle recession of nearly 180 degrees of the lower circumference was observed.

In all patients reported to suffer from hyphema, or angle recession, or both, after being exposed to nearby explosion, foreign bodies were found in cornea or eyelids, or corneal lacerations were observed.[2-4] The resulting damage in these cases was thought to be a consequence of both the pressure wave and the effect of the foreign body.[4]

In a case report[5] of injuries caused to various parts of the eye by exploding letter bombs, propagation of high-pressure wave in the anterior chamber was believed to cause damage, although in all three patients foreign bodies, or contusion of the eyeball by a solid object, or both, were clearly evident, and there was no way to differentiate the effect of the blast from the contribution of the foreign body/contusion to the ocular damage.

Our case is unique because the ocular damage in this instance was the result of blast injury alone. No foreign body or blunt trauma to the eye by any solid object was found. The presence of blast wave was clearly proven by the auditory blast injury caused to three other persons standing close to our patient at the moment of explosion.

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Mild Frosted Branch Periphlebitis

David J. Browning, M.D.

Inquiries to David J. Browning, M.D., 1600 E. Third St., Charlotte, NC 28204.

In 1976, frosted branch periphlebitis was first described as a bilateral retinal vasculitis in a 6-year-old boy.[1] Subsequent reports have defined the syndrome as involving otherwise healthy young patients with variable degrees of iritis and vitreitis, dramatic venous sheathing, variable degrees of retinal hemorrhage and edema, optic disk edema, and marked permeability of retinal veins on fluorescein angiography.[2,3] Laboratory study results are generally normal. Sugin and associates[4] enlarged the description of the syndrome by reporting two unilateral cases. All of these authors[1-4] have treated and emphasize the need to treat patients with systemic corticosteroids to reverse and prevent possible visual loss. I encountered a unilateral case in which no systemic corticosteroids were used and in which the outcome was excellent, suggesting a broader spectrum of severity than previously reported in this disease.

A 28-year-old woman was seen on Nov. 1, 1988, because of a two-month period of floaters and photopsias in the left eye. She was in good general health with no previous viral syndrome. She took oral contraceptives. Visual acuity was 20/20 in each eye. Applanation tensions were 18 mm Hg. There were no afferent pupillary defects. Slit-lamp examination was remarkable only for mild anterior vitreous cells in the left eye. The right eye was normal. In the left eye, disk edema and prominent venous sheathing were present ophthalmoscopically. A fluorescein angiogram showed marked late venous leakage and disk staining (Fig. 1). Normal laboratory studies included chest x-ray, angiotensin-converting enzyme, antinuclear antibody, serologic test for syphilis, fluorescent treponemal antigen-antibody, and lupus anticoagulant. Erythrocyte sedimentation rate was 36 mm/hr (normal, < 10 mm/hr). Epstein Barr virus antibody titers were: IgG 1:2,560, IgM negative, EA 1:10, and EbNa 1:8. Cytomegalovirus titers were: IgG 1:3, IgM 1:10. A diagnosis of frosted branch periphlebitis was made and observation only was recommended.

On Nov. 23, 1988, the patient returned complaining of increasing floaters. Examination disclosed increased vitreous cellular infiltrate and venous sheathing. A subconjunctival injection of 30 mg of triamcinolone acetonide was given. No change in symptoms occurred, but

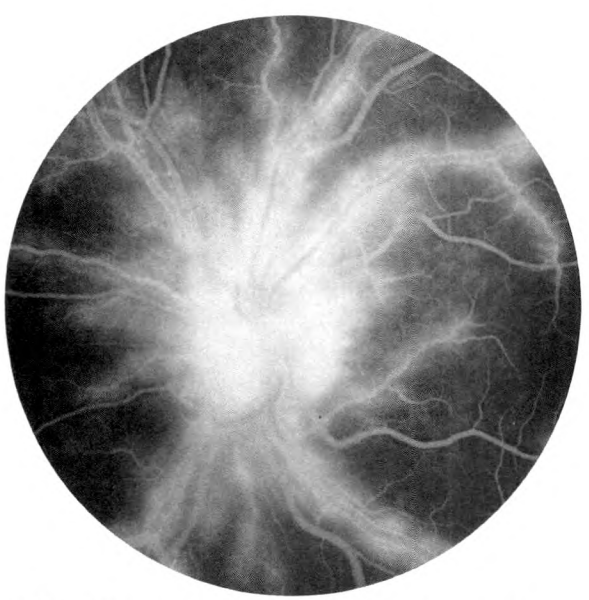


Fig. 1 (Browning). Fluorescein angiogram shows extensive venous leakage of fluorescein and increased disk staining.

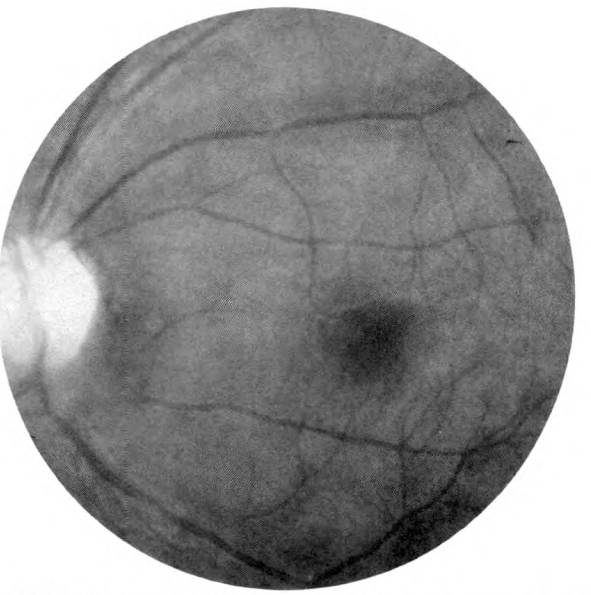


Fig. 2 (Browning). Fundus photograph of the left eye three years later shows regression of venous sheathing and disk edema.

gradually over the next three years the disk edema and venous sheathing resolved (Fig. 2) without any further therapy.

Previous reported cases of frosted branch periphlebitis feature patients with acute visual loss treated with systemic corticosteroids.[1-4] Sugin and associates[4] emphasized the early institution of systemic corticosteroid therapy to prevent macular scarring. My patient's course broadens the concept of the disease. Frosted branch periphlebitis need not cause reduced visual acuity. In such cases, a single periocular corticosteroid injection, or perhaps the course of the disease, is compatible with an excellent visual outcome.

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Retinal Neovascularization and Cystoid Macular Edema in Punctata Albescens Retinopathy

Shimon Rumelt, M.D., Eliezer Kraus, M.D., and Uri Rehany, M.D.

Department of Ophthalmology, Western Galilee Regional Medical Center-Nahariya.

Inquiries to Uri Rehany, M.D., Department of Ophthalmology, Western Galilee Regional Medical Center-Nahariya, POB 21, 22100 Nahariya, Israel.

Punctata albescens retinopathy is an inherited retinal disease characterized by multiple discrete white dots at the level of the retinal pigment epithelium.[1] A gradual constriction of visual fields and nyctalopia are found in these patients along with accordingly affected results of electroretinography. Fluorescein angiography discloses multiple window defects without fluorescein leakage. We encountered a patient with the unusual combination of cystoid macular edema and retinal neovascularization.

A 13-year-old white girl complained of bilateral gradual decrease in vision and a central gray scotoma of eight months' duration at initial examination. She had hyperopia of 5 diopters and her best-corrected visual acuity was 20/60. Ophthalmoscopy disclosed bilateral numerous symmetric white dots, scattered at the periphery and midperiphery of the retina (Fig. 1, top and bottom). These lesions (0.1 to 0.3 disk diameter) were confluent near the vascular arcades and spare toward the periphery. A few foci of retinal neovascularization were found 2 disk diameters from the optic nerve head in both eyes (Fig. 1, right). Besides progressive nyctalopia, there was no history of any other ocular or systemic disease.

A visual field of 10-degree concentric constriction was found. Fluorescein angiography disclosed numerous areas of subretinal leakage corresponding to the flecks and at the late phase, cystoid macular edema was obvious. Fluorescein leakage was seen from the retinal neovascularization (Fig. 2). Light and dark adaptation electoretinography was extinguished.

The patient's retinal edema resolved after treatment with acetazolamide, 250 mg, four times a day, for one month; but the cystic macular changes remained and visual acuity was not improved.

The patient's sister had the same clinical ophthalmoscopic and electrophysiologic findings of punctata albescens retinopathy, excluding retinal neovascularization and cystoid macular edema. Examination of the parents did not disclose any ocular or systemic abnormality, thus proposing an autosomal recessive trait.

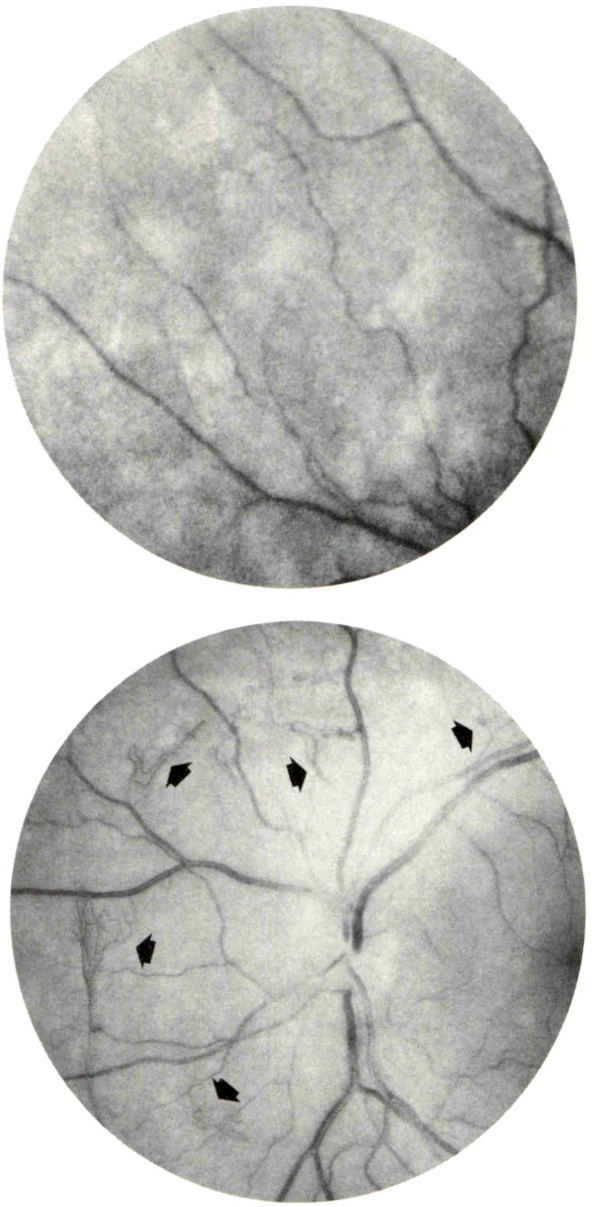


Fig. 1 (Rumelt, Kraus, and Rehany). Ophthalmoscopic appearance of the left eye showing white subretinal flecks. The superonasal peripheral zone (top) and the posterior pole (bottom). Several new vessels in the retina are seen 2 disk diameters from the optic disk (arrows).

Punctata albescens retinopathy is a form of retinitis pigmentosa that has a similar clinical course and may be familial.[2] The ophthalmoscopic appearance differs in the lack of subreti-

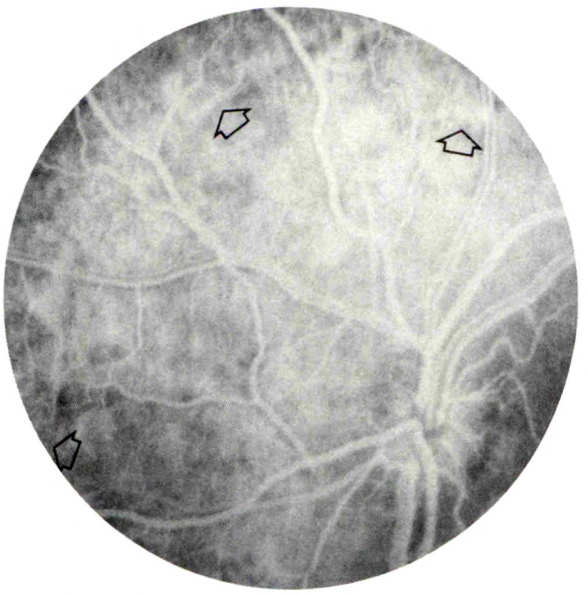


Fig. 2 (Rumelt, Kraus, and Rehany). Early venous phase of retinal angiogram showing the posterior pole with multiple retinal new vessels (arrows).

nal pigment clumps in punctata albescens retinopathy and the finding of numerous, white, discrete subretinal dots. Punctata albescens retinopathy has been suggested as an earlier stage of retinitis pigmentosa, which implies that pigmentary changes may appear later in patients who have white subretinal flecks.[1]

Although cystoid macular edema may be found in up to 23% of patients with retinitis pigmentosa,[3] and retinal neovascularization may appear in some patients,[4] these findings would be unusual in the punctata albescens retinopathy form.

Our findings suggested that similar clinical manifestations may appear early in the course of the disease and cause a central scotoma as an initial symptom. The presence of retinal neovascularization and subretinal leakage in punctata albescens retinopathy and retinitis pigmentosa contributes further evidence that these two entities may have similar manifestations and that the underlying pathophysiologic characteristics may be the same. Abnormal metabolism of the retinal pigment epithelium may be assumed to weaken this site, thus allowing subretinal leakage.

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Subretinal Diathermy Probe

Gholam A. Peyman, M.D., and Nalin J. Mehta, M.D.

LSU Eye Center, Louisiana State University Medical Center School of Medicine. Supported in part by United States Public Health Service grants EY07541 and EY02377 from the National Eye Institute, National Institutes of Health, Bethesda, Maryland. Dr. Peyman has a proprietary interest in the instrument.

Inquiries to Gholam A. Peyman, M.D., LSU Eye Center, 2020 Gravier St., Suite B, New Orleans, LA 70112-2234.

With the advent of submacular surgical removal of choroidal neovascular membranes in appropriate cases of macular degeneration, efficient and limited hemostasis in the subretinal space becomes necessary to limit surgical morbidity.[1-3]

We have designed a new subretinal diathermy probe for subretinal coagulation of bleeding vessels in surgical cases involving age-related macular degeneration and presumed ocular histoplasmosis syndrome (Figure). The new probe consists of a 23-gauge, right-angled coaxial bipolar diathermy tip 1.5 × 2.5 mm in dimension. The probe is insulated except for a small section on the underside of the distal portion, 0.75 mm from the tip. This area provides focal diathermy confined to the underside of the probe. The proximal end of the probe inserts into a standard diathermy handpiece.

The new probe has been successful in submacular procedures. Intravitreal diathermy is performed using the tip of a straight probe. In order to coagulate bleeding choroidal vessels, the retina must be elevated substantially from the surface of the retinal pigment epithelium. Accuracy of diathermy is limited by the noninsulated area of the tip, which may inadvertently coagulate the sensory retina. The advantage of our subretinal probe is its ability to focus diathermy energy toward the retinal pigment epithelium and choroid while insulating overlying sensory retina. The limited active area of the probe confines coagulation to the points of

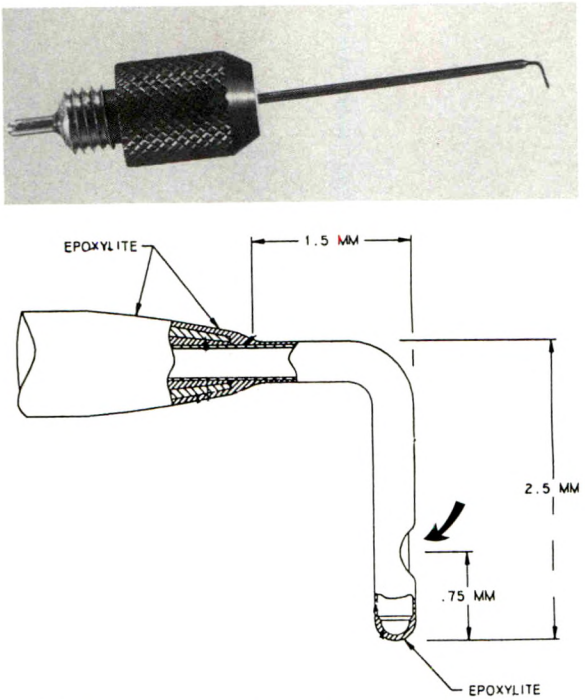


Figure (Peyman and Mehta). Top, Subretinal diathermy probe. Bottom, Schematic diagram of diathermy probe tip. Arrow points to area of noninsulated electrode actually used during diathermy. Epoxylite is used for insulation.

choroidal bleeding. Access to the subretinal space can be made through the retinotomy already provided for submacular net removal; enlargement is not necessary. Further, the diathermy tip forms a pick that can be used for delicate subretinal tissue manipulation, especially separation of the retina from the underlying neovascular net.

The subretinal diathermy probe should enhance the surgeon's ability to perform subretinal coagulation with limited tissue damage, thereby improving the patient's visual prognosis.

ACKNOWLEDGMENT

The subretinal diathermy probe was developed in collaboration with MIRA, Inc., Waltham, Massachusetts.

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Idiopathic Alternating Anisocoria

Michael C. Brodsky, M.D., Gregory B. Sharp, M.D., Katherine J. Fritz, B.S., and James J. Corbett, M.D.

Departments of Ophthalmology (M.C.B., K.J.F.) and Neurology (G.B.S.), University of Arkansas for Medical Sciences; and Department of Neurology (J.J.C.), University of Mississippi School of Medicine. Supported in part by a grant from Research to Prevent Blindness, Inc., New York, New York.

Inquiries to Michael C. Brodsky, M.D., Arkansas Children's Hospital, 800 Marshall, Little Rock, AR 72202.

Alternating anisocoria (mydriasis a bascule) is a rare condition in which the pupils dilate in alternating fashion and often show a poor or absent light reflex during the dilation phase.[1] We studied this phenomenon in a neurologically normal boy.

A 15-year-old boy, referred to Arkansas Children's Hospital, had a two-week history of alternating anisocoria. He had no history of recent head trauma or viral illness. Hypothyroidism had been recently diagnosed and the patient was taking levothyroxine orally. Over the previous six months, he had been hospitalized at a private psychiatric hospital for a behavior disturbance. He frequently took antihistamines orally for allergies.

Corrected visual acuity was 20/30 in each eye. The right pupil was 4.5 mm and the left pupil was 6.5 mm in room light (Figure, top). Each pupil constricted briskly to light and there was no afferent pupillary defect. In darkness, each pupil redilated briskly, and a 2-mm anisocoria persisted. There was no blepharoptosis or anhidrosis to suggest a Horner's syndrome in either eye. After two hours, the left pupil constricted to 4.5 mm and the right pupil dilated to 5.5 mm over five minutes (Figure, bottom). This anisocoria persisted for two hours before it again reversed. Slit-lamp examination showed

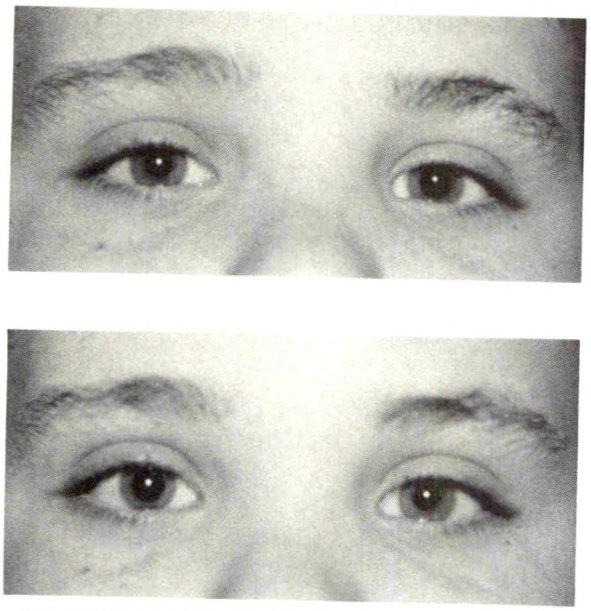


Figure (Brodsky and associates). Top, Anisocoria in which left pupil is larger than right. Note symmetry of palpebral fissures. Bottom, Two hours later right pupil is larger than left.

round pupils and normal pupillary ruff with no evidence of segmental contracture in either eye. Results of a neurologic examination were normal. Results of a magnetic resonance scan of the head were normal. Follow-up observation over a six-month period showed persistent alternating anisocoria two to four times daily.

In a review of 128 normal subjects, ages 8 to 92 years, Lam, Thompson, and Corbett[2] found a 19% point prevalence of simple anisocoria (defined as a difference in pupillary diameter of 0.4 mm or more). When each subject was observed twice daily for five days, the incidence of anisocoria was 38%. In any given subject, the larger pupil was always in the same eye, and the largest pupillary inequality was 0.8 mm. Loewenfeld[3] described two patients with anisocoria in whom a 0.5-mm reversal was observed, and argued that such reversal was within the realm of simple central anisocoria. Kline, McCluer, and Bonikowski[4] described alternating anisocoria from oculosympathetic spasm in a quadriplegic patient with a posttraumatic syringomyelic cyst. The patient displayed asymmetric pupillary mydriasis upon passive elevation or stretch of an arm or leg.[4] Elevation of either arm produced more dilation in the ipsilateral pupil, while elevation of a leg produced more dilation in the contralateral pupil. Close examination disclosed widening of the palpebral fissure on the side of the larger pupil.

Alternating anisocoria has been attributed to central sympathetic activity; however, in our patient there was no associated blepharoptosis, eyelid retraction, change in sweating, or conjunctival vasodilation to suggest an abnormality of oculosympathetic innervation. Our patient's pupils constricted normally to light and dilated briskly in darkness, which suggests that this unusually large, alternating anisocoria falls within the spectrum of physiologic anisocoria. Despite its seemingly ominous clinical manifestation, our patient's alternating anisocoria proved to be neurologically inconsequential.

Alternating anisocoria without associated signs of oculosympathetic involvement could hypothetically be caused by periodic constriction of one pupil resulting from stimulation of the iris sphincter muscle, or from periodic dilation of one pupil as the sphincter muscle is being inhibited. Such an effect would have to be mediated at the level of the Edinger-Westphal nucleus, although the underlying mechanism by which central parasympathetic innervation would be unilaterally altered is unclear.

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Inflammatory Orbital Tumor as an Ocular Sign of a Battered Child

William Waterhouse, M.D., Robert W. Enzenauer, M.D., and Vernon C. Parmley, M.D.

Retina-Vitreous Service (W.W.) and Pediatric Ophthalmology Service (R.W.E.), Fitzsimons Army Medical Center; and Cornea and External Disease Service (V.C.P.), Madigan Army Medical Center. The assertions or opinions contained herein are the private

views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Inquiries to Robert W. Enzenauer, L.T.C., M.C., Pediatric Ophthalmology Service, Fitzsimons Army Medical Center, Aurora, CO 80045.

Physical child abuse frequently results in considerable injury and occasionally in death. The head is the most common target in physical abuse. Facial involvement with ocular signs has been reported in up to one half of the cases.[1-5] We treated an infant referred for ophthalmic examination of a rapidly growing inflammatory orbital mass resulting from physical abuse.

The infant had been a full-term uncomplicated vaginal birth with normal Apgar scores. The infant's social history was remarkable for separation of the parents secondary to incompatibility. The patient was first seen by the referring ophthalmologist at 2 weeks of age because of an ecchymotic area over the left inferior eyelid with minimal associated eyelid edema. The mother described an erythematous, intermittently exacerbating rash over the left eyelid from birth. No intervention was initiated at this time. At 1 month of age, the infant was admitted to the local emergency room with evidence of a hemorrhagic conjunctivitis. Conservative therapy was initiated with topical antibiotics. A few days later, the patient was again admitted with a hemorrhagic mass protruding from his medial left lower eyelid. Computed tomography disclosed posterior extension of the mass with inflammation (Fig. 1). The crystalline lens was also noted to be absent in the left eye. Orbital rhabdomyosarcoma was suspected, but biopsy of the mass disclosed only inflammation and an organized clot. At this time, the child was referred for further examination and treatment.

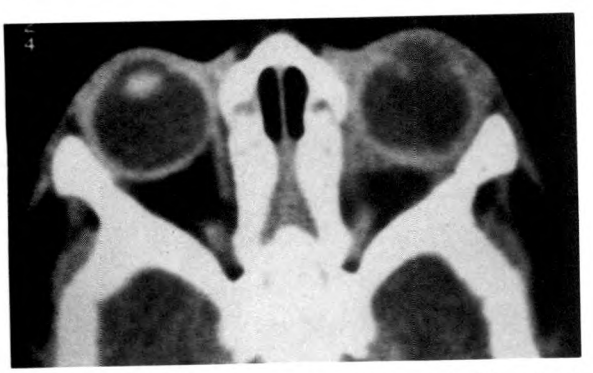


Fig. 1 (Waterhouse, Enzenauer, and Parmley). Computed tomographic scan of the head and orbits disclosing retro-orbital extension of the mass.

An examination with the child under anesthesia at the referring institution showed erythematous conjunctiva without evidence of an anterior mass. The cornea was inflamed with a hazy infiltrate, especially in the inferotemporal quadrant, and the iris was missing between the three and six o'clock meridians. The crystalline lens was not visualized. Vitreous hemorrhage prevented visualization of the posterior segment of the globe.

The consulting ophthalmologist believed the patient's findings were most consistent with trauma and a healing globe penetration. When initially confronted with this possibility, the mother offered no explanation for the child's injuries. An examination for physical abuse was initiated. A bone scan showed fractures of the right seventh and eighth ribs, and an epiphyseal fracture of the distal right femur (Fig. 2). When confronted with this additional evidence, the mother eventually admitted to hitting her child with a stick.

Physical abuse must be suspected when the history or the extent of injury is not consistent with the physical findings or the age and developmental level of the child.[1] Mandatory reporting laws currently exist in all 50 states, and most states offer immunity from criminal prosecution and civil liability to those reporting in

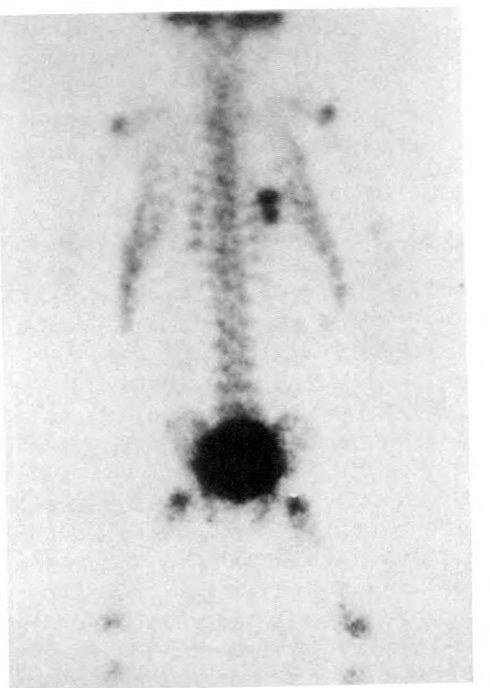


Fig. 2 (Waterhouse, Enzenauer, and Parmley). Bone scan showing obvious rib fractures on the right.

good faith. Ophthalmologists need to be aware of the syndrome of the battered child, as they may be the first to examine a physically abused child. Prompt recognition is urgent to minimize morbidity and mortality for the child and to initiate therapy for the offending adult.

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Malignant Myoepithelioma After Radiation for Retinoblastoma

Stephen J. Saxe, M.D., Hans E. Grossniklaus, M.D., and Ayten O. Someren, M.D.

Departments of Ophthalmology (S.J.S. and H.E.G.) and Pathology (H.E.G. and A.O.S.), Emory University School of Medicine.

Inquiries to Hans E. Grossniklaus, M.D., L. F. Montgomery Ophthalmic Pathology Laboratory, Emory Eye Center, 1327 Clifton Rd. N.E., Atlanta, GA 30322.

Salivary gland neoplasms composed of myoepithelial cells, whether benign or malignant, are extremely rare.[1] It is well established that radiotherapy of the head and neck can initiate the development of many neoplastic lesions.[2] There is strong evidence to suggest that the development of a second nonocular neoplasm in patients with heritable retinoblastoma results from a germinal mutation.[3] We managed a case of malignant myoepithelioma of the parotid gland that developed after irradiation for heritable retinoblastoma.

A 15-year-old girl had had bilateral heritable retinoblastomas diagnosed when she was 15 months old. At the time of diagnosis, the left eye was enucleated. The right eye was treated with radiation and chemotherapy. The retinoblastoma in her right eye regressed and the patient did well until she was 15 years old. She was examined at that time because of a one-month history of an enlarging mass over her right zygomatic bone in the parotid gland and preauricular area. Computed tomography showed that the mass had invaded the inferotemporal wall of the orbit (Fig. 1). A biopsy of the mass showed an invasive, poorly differentiated malignant neoplasm apparently originating from the parotid gland. Immunohistochemical stains were positive for cytokeratins, vimentin, desmins, S-100 protein, and muscle-specific actin in tumor cells (Fig. 2). Electron microscopy showed basement membrane production, microvilli, intercellular junctions, and intracytoplasmic actin filaments in tumor cells. The diagnosis was malignant myoepithelioma supported by immunohistochemical and ultrastructural findings similar to previous cases.[1,4] The patient was treated with systemic chemotherapy that consisted of vincristine, doxorubicin, and cyclophosphamide. She later developed distant metastases and died 13 months after the malignant myoepithelioma of the parotid gland was diagnosed.

There are two lines of evidence to suggest the tumor in this case was related to radiotherapy and the initial retinoblastoma. First, there is

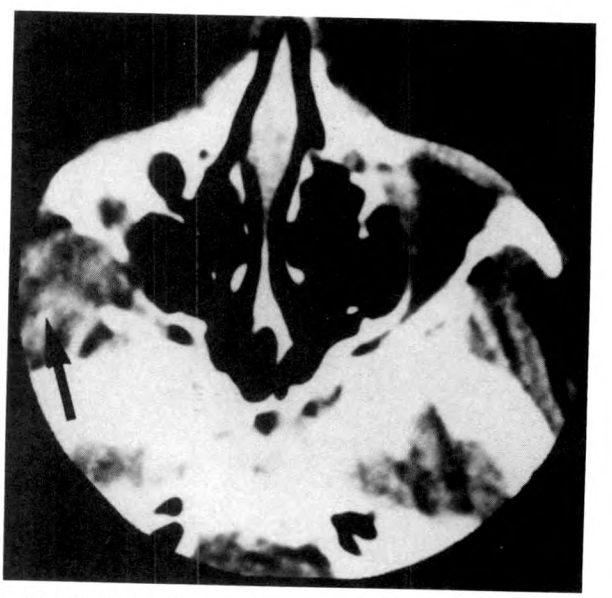


Fig. 1 (Saxe, Grossniklaus, and Someren). A soft-tissue mass (arrow) invades the inferolateral wall of the right orbit.

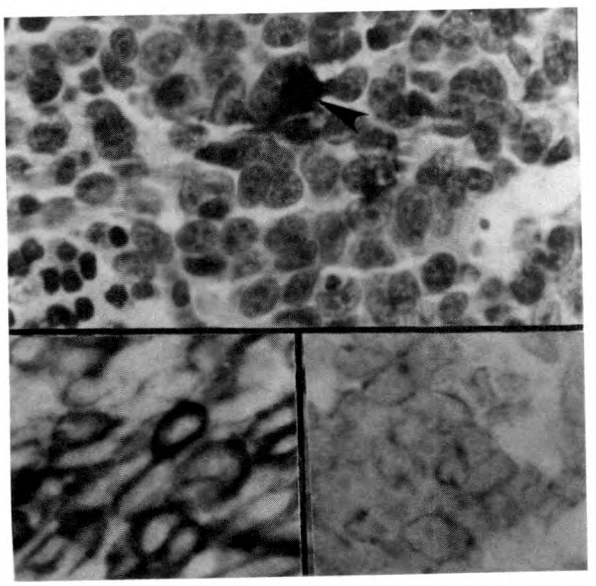


Fig. 2 (Saxe, Grossniklaus, and Someren). Top, The cytoplasm in occasional tumor cells (arrowhead) stains positive for S-100 protein (peroxidase antiperoxidase, ×160). Bottom left, Tumor cells strongly stain for muscle-specific actin (peroxidase antiperoxidase, ×160). Bottom right, Focal intracytoplasmic-positive staining for low-molecular-weight cytokeratins is present in tumor cells (peroxidase antiperoxidase, ×160).

strong evidence to suggest the genetic mutation, which results in bilateral retinoblastoma and 15% of unilateral cases, is a major factor that causes an increased incidence of second nonocular tumors.[3] Second, it has been well established that radiotherapy of the head and neck initiates neoplastic lesions.[2] These two factors combined with the findings that the latency period for parotid gland lesions varies from five to 35 years[5] and that the mean latency period for the appearance of a second primary tumor in patients with bilateral retinoblastoma is 13 years[3] support the hypothesis. Possibly radiation to tissue genetically predisposed to develop a neoplasm resulted in the malignant myoepithelioma in our case.

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Periosteal Flap for Lower Eyelid Reconstruction

Charles R. Leone, Jr., M.D.

Department of Ophthalmology, University of Texas Health Science Center.

Inquiries to Charles R. Leone, Jr., M.D., 7950 Floyd Curl Dr., Suite 505, Medical Center Tower 1, San Antonio, TX 78229.

When the lateral aspect of the lower eyelid is removed and reapproximation to the lateral rim is impossible, particularly with recurrent tumors, a method must be used to reconstruct the eyelid. To avoid borrowing tarsoconjunctiva from the upper eyelid, a temporal-zygomatic skin flap lined on the inside by conjunctiva can be mobilized, but the eyelid may lack sufficient support and may sag. I have used a technique in which the reconstructed eyelid was connected to the lateral canthus by using the lateral orbital rim periosteum as a sling and a temporal skin flap.

With the periosteal flap technique, after it is determined that the medial end of the resected eyelid cannot be approximated to the lateral canthus, the lateral rim is exposed. Just above the level of the lateral canthal angle, periosteum is incised on the anterior surface in a rectangular manner with the base at the inner aspect of the lateral rim. The vertical width is at least 5 mm and the horizontal length conforms to the length necessary to reach the eyelid segment, usually 1 cm in length (Fig. 1). This flap is mobilized carefully with sharp and blunt dissection by using the tip of a sharp periosteal

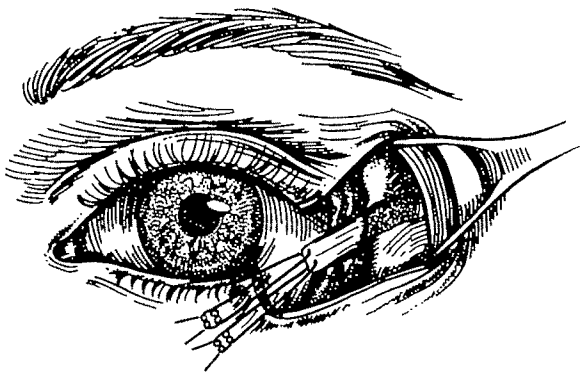


Fig. 1 (Leone). The lateral orbital rim is exposed and the periosteal flap is incised, 5 mm in width and with the length corresponding to the defect. With the flap hinged on the inner aspect of the rim, it is sutured to the tarsus of the remaining eyelid with 6-0 polyglactin.

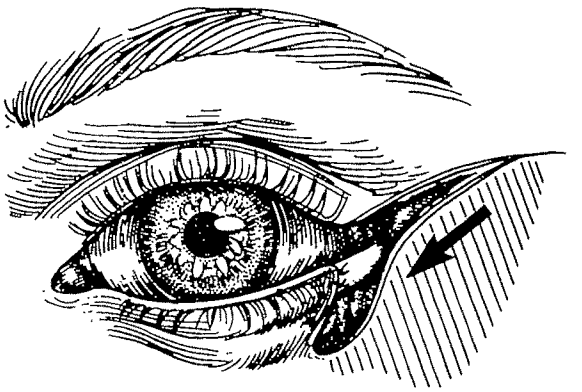


Fig. 2 (Leone). The temporal skin flap is extended over the orbital rim with a slightly superior curve and is undermined (oblique lines) to the inferior aspect of the eyelid excision to allow rotation (arrow) into the defect.

elevator to separate the periosteum from the bone. It is necessary to begin slightly above the level of the canthal angle to give an upward direction or curve to the lower eyelid. The free end of the sling is sutured to the free eyelid segment with interrupted sutures of 6-0 polyglactin, while making certain there is enough tension to approximate the eyelid snugly to the globe. If it is too loose, the periosteal sling should be trimmed. To mobilize the skin flap, an incision is made at the canthal angle toward the end of the brow and then into the temporalis muscle fossa for approximately 2 to 3 cm (Fig. 2). This flap is undermined to the level of the inferior aspect of the eyelid resection to facilitate medial movement of the skin-flap segment. If mobilization is difficult, the skin flap can be extended. The medial edge of the skin flap is sutured to the eyelid segment with interrupted sutures of 6-0 polyglactin, and the superior edge of the flap is sutured to the periosteal sling with interrupted sutures of 6-0 plain catgut with the knots pulled toward the skin surface.

The use of lateral rim periosteum as slings or extensions for upper and lower eyelid reconstruction for congenital absence of eyelids[1] or after extensive lateral canthal excision[2] has been described. I have successfully used this technique in eight patients and there has been no incidence of foreign-body sensation and all patients have healed without complication. In the postoperative period, the periosteum is epithelialized after several months. The firmness of the periosteal flap keeps the lower eyelid in the desired position and maintains the upward curve, as well as supporting the eyelid in general. This technique also obviates using tarsoconjunctiva from the upper eyelid, which makes the procedure less complicated and reduces potential morbidity.

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Correspondence

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Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Frosted Branch Angiitis Associated With Cytomegalovirus Retinitis

EDITOR:

In the article, "Frosted branch angiitis associated with cytomegalovirus retinitis," by R. F.

Spaide, A. T. Vitale, I. R. Toth, and J. M. Oliver (Am. J. Ophthalmol. 113:522, May 1992), the authors state that the use of corticosteroids in patients suffering from frosted branch angiitis, cytomegalovirus retinitis, and acquired immunodeficiency syndrome is contraindicated. They state that, ". . . had severe immunosuppression from AIDS and cytomegalovirus infection, which contraindicates the use of corticosteroids."

There is consensus that corticosteroids are indicated as adjunctive treatment for *Pneumocystis carinii* pneumonia in patients with AIDS.[1] Beneficial effects of corticosteroid therapy were reported for HIV-related immune thrombocytopenia[2] and severe HIV-associated myositis,[3] and corticosteroids seem to be effective in toxoplasmosis-induced cerebral edema in patients with AIDS. Corticosteroid-related development of Kaposi's sarcoma in patients with AIDS was reported,[4] but this observation was not replicated.[1] We are not aware of any replicated findings demonstrating that corticosteroids in principle are contraindicated in patients with AIDS. Therefore, there is considerable evidence that corticosteroids are indicated in patients with AIDS and particular diseases.

Recently, we encountered a case of frosted branch angiitis in a patient with cytomegalovirus retinitis, cerebral toxoplasmosis, and AIDS.[5] The patient was treated with intravenously administered ganciclovir (10 mg/kg of body weight per day) and oral fluocortolone (100 mg/day initially). Vascular sheathing disappeared promptly, and visual acuity improved from 20/200 to 20/30. After two weeks, fluocortolone was reduced stepwise to 20 mg/day. Cytomegalovirus retinitis resolved, and scar formation was observed. The patient retained a visual acuity of 20/30 without relapse of cytomegalovirus retinitis on ganciclovir maintenance treatment (6 mg/kg of body weight per day intravenously) during a nine-month follow-up period. Additionally, the patient was treated for cerebral toxoplasmosis with pyrimethamine, 75 mg/day; clindamycin, 2 to 4 g/day; and folinic acid, 15 mg/day. No retinal detachment was observed, and we encountered no corticosteroid-related adverse effects in our patient.

Because of the reports in the literature on the use of corticosteroids in patients with AIDS and because of our own experience we do not agree with Spaide and associates that corticosteroids are contraindicated in patients with frosted branch angiitis and AIDS. By weighing risks and benefits, corticosteroids might be effective and necessary as adjunctive treatment in patients with frosted branch angiitis suffering from AIDS and cytomegalovirus retinitis. We believe adjunctive treatment with corticosteroids might also be indicated in patients with AIDS and sight-threatening ocular toxoplasmosis.

STEPHAN A. GEIER, M.D.
JOACHIM NASEMANN, M.D.
VOLKER KLAUSS, M.D.
URSULA KRONAWITTER, M.D.
FRANK D. GOEBEL, M.D.
Munich, Germany

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Reply

EDITOR:

We appreciated the comments by Dr. Geier and associates, and have read their case report[1] with great interest. Although certain conditions associated with AIDS may be helped by the use of corticosteroids, the specific question is whether corticosteroids are indicated for frosted branch angiitis associated with cytomegalovirus retinitis. Our article summarized the findings in the first three patients we encountered with this particular condition;

since then we have seen three additional patients. Each of these patients had severely decreased CD4 T-cell counts and the frosted branch angiitis was noticed only on initial manifestation of the cytomegalovirus retinitis. All of the patients had rapid clearing of the inflammatory sheathing around the retinal vessels with specific antiviral treatment. Of interest is that our patients who did not have direct infection of the macula had few complaints about their visual acuity.

As we mentioned in the discussion, the inflammatory changes around the vessels may be caused either by direct infection around the vessels or by immune-complex deposition. Subsequent inflammatory manifestations occurring in either situation could create the frosted appearance around the blood vessels. We stated that reduction of either the antigen load or the immune response could be expected to reduce the resultant inflammatory sheathing around the vessels. In our experience, the frosted branch angiitis responded quickly to specific antiviral treatment. Additionally, as mentioned in our article, these patients have to be examined for syphilis and tuberculosis, which are known causes for retinal vasculitis in AIDS patients. Since the examination for these infections may take days or weeks, prompt treatment with corticosteroids may prove to be unnecessary or detrimental. Dr. Geier and associates did not mention if their patient was examined for syphilis or tuberculosis. Their patient did have toxoplasmosis, however.

Because these patients have severe immune suppression, corticosteroids reduce the immune response without inhibiting cytomegalovirus replication, and there is specific antiviral treatment available, the use of corticosteroids does not seem to be specifically indicated. Only a randomized trial could determine the incremental benefit corticosteroids might add in the treatment of frosted branch angiitis associated with cytomegalovirus retinitis, however.

RICHARD F. SPAIDE, M.D.
ALBERT T. VITALE, M.D.
ILONA R. TOTH, M.D.
JORGE M. OLIVER, M.D.
New York, New York

Reference

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Ultrasound Biomicroscopy of Anterior Segment Structures in Normal and Glaucomatous Eyes

EDITOR:

In the article, "Ultrasound biomicroscopy of anterior segment structures in normal and glaucomatous eyes," by C. J. Pavlin, K. Harasiewicz, and F. S. Foster (Am. J. Ophthalmol. 113:381, April 1992), the authors describe an ultrasound diagnostic technique that is bound to have important and interesting applications because it visualizes a third dimension of the angle structures, which until now was mainly a two-dimensional world.

I would like to comment on one of the 15 baseline measurements collected by the authors from normal eyes. The authors have measured the extent of iris-lens contact. The figures given are essentially artifactual for the following reasons.

The iris approach to the anterior lens surface near the pupil has the shape of a sharp cuniform with slightly curved front and back sides, especially so if the pupil is small. As these two sides get closer centrally, a point is reached where the distance separating them is below the resolving power of the ultrasound and imaging equipment. Consequently the apparent iris-lens contact will seem to extend more peripherally than is actually the case. The iris-lens contact could still have some value of a comparative nature if the pupil size is also taken into consideration.

I would like to make a second point with regard to iris-lens contact. Aqueous humor cannot leave the posterior chamber if there is iris-lens contact in all meridians at all times. If, for the sake of simplifying matters, this outflow is considered to occur at a continuous rate of flow, aqueous production at 2.5 mm^3 per minute can leave the posterior chamber through an iris-lens separation of the order of 1 to 2 μm if there is a 4-mm pupil and a presumptive pressure differential of 1 mm Hg. This iris-lens separation is well below the resolving power of the equipment used so that it will not be visualized. In reality, I believe the aqueous leaves the posterior chamber in squirts synchronous with the systolic pulse of

the intraocular vascular mass. There should therefore exist a rhythmic, clinically imperceptible and alternating iris-lens touch and separation. The phase of iris-lens contact should be longer than the duration of the iris separation and the iris movement during the latter would blur the ultrasound image. Overall, the authors would select the sharper images that would tend to be scanned during true iris-lens contact. The squirting action can be observed at the slit lamp. If suspended cellular elements are present in the aqueous their movement can be observed as they leave the posterior chamber near the pupillary margin. These particles, apart from a continuous smooth motion caused by convection currents, also move in rhythmic jerks.

ALBERT M. BEZZINA, M.D.
Pavia, Italy, and M'scala, Malta

Reply

EDITOR:

We agree with Dr. Bezzina that our measurements of iris-lens contact have to be interpreted with awareness of the resolving power of the instrument involved. We used the absence of a discernible separation between the iris and lens as the end points for these measurements. Axial resolution would be approximately 40 m m for the transducer used. It is possible, indeed probable, that a small separation below this resolution would be missed.

At no time in our studies did we observe a complete separation of the iris from the lens surface. This may have been caused by flow through a space below the resolution of the transducer used, or it could have been because lifting of the iris occurred intermittently and at a time when we were not observing it. Since the frame rate used (five frames per second) is not in true real time, subtle rapid fluctuations could be missed. There is, unfortunately, no easy way to resolve this issue. Further technical refinements in the instrumentation, such as a more rapid frame rate and increased resolution, would be helpful. We do, however, believe our method has the highest currently available resolution and, given the limitations described, adds new insight into the iris-lens relationship creating a basis for future comparison of normal individuals and patients with glaucoma that has not been available.

CHARLES J. PAVLIN, M.D.
KASIA HARASIEWICZ, P. Eng.
F. STUART FOSTER, Ph.D.
Toronto, Ontario, Canada

BOOK REVIEWS

Edited by Mark J. Mannis, M.D.

Grayson's Diseases of the Cornea, ed. 3. By Robert C. Arffa. Philadelphia, Mosby Year Book, 1991. 725 pages, index, illustrated. $169

Reviewed by RONALD D. PLOTNIK
Rochester, New York

The preface to the third edition of this classic work describes the goals of the author: readability, single authorship, clinical orientation, a high number of quality illustrations, and the use of tables. It further states that the intended readership includes ophthalmology residents and the general ophthalmologist. Dr. Arffa has achieved these objectives remarkably well.

Grayson's Diseases of the Cornea provides a review of corneal and external disease that is primarily clinical and practical. The text begins with a review of anatomy and physiology of the cornea, conjunctiva, eyelids, and tear film. Although not comprehensive, the review contains excellent clinical correlations, numerous photographs, and well-drawn diagrams. The chapter on history and examination is fairly complete. It describes both simple and more complex examination techniques. Additionally, it includes differential diagnoses for various signs including cornea verticillata, crystalline keratoplasty, vascularization, and punctate keratitis. The chapter on laboratory evaluation is an informative review of cytologic techniques and their interpretation as well as culture, biopsy, and impression cytology techniques.

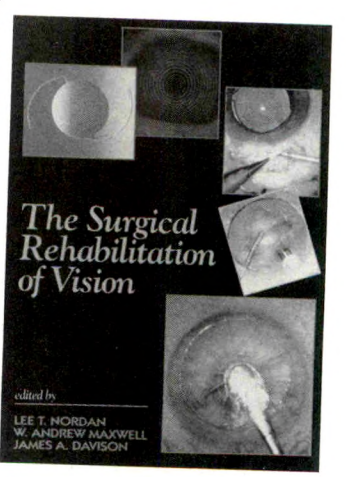
The remaining chapters deal with the broad range of corneal and external disease. Congenital anomalies are reviewed in detail with many associated diagrams. Follicular, neonatal, and bacterial conjunctivitis are well covered in a multi-page table that details conjunctival and corneal signs, cytologic findings, etiologic factors, and other pertinent information. Noninfectious conjunctivitis is covered less thoroughly but is well organized and readable. Thorough tables relating to bacterial keratitis include such information as likely organisms, broad-spectrum initial antibiotic coverage, preparation of fortified topical antibiotics, preparation of subconjunctival antibiotics, and approaches to antibiotic choice. The chapter on viral diseases is clear, directed, and specific. A construct of appropriate treatment for infectious and immune-related manifestations of herpes simplex is particularly straightforward and useful.

The chapters on corneal degenerations and dystrophies are a pleasure to read. Although not comprehensive, they are filled with illustrative designs and photographs. Primary and systemic immunologic disorders are well covered. Chapters are included on endocrine disorders, disorders of lipid and carbohydrate metabolism, and other metabolic abnormalities. The survey of primary skin disorders with ocular effects is useful as are the sections on drugs and toxic and allergic reaction to topical medications.

Overall, the goals of the author have been exceptionally well met. Residents and general ophthalmologists will find this a readable, informative, and friendly text. For those wishing more extensive or source information, for those who specialize in corneal and external disease, for those wishing a review of the basic science literature, or for those interested in the cutting edge information, this is not the appropriate text. I would guess, however, that even these individuals will benefit from this useful book during the course of daily practice.

The Surgical Rehabilitation of Vision. Edited by Lee T. Nordan, W. Andrew Maxwell, and James A. Davison. New York, Raven Press, 1992. 375 pages, illustrated. $125

Reviewed by ERICH GROOS
Nashville, Tennessee



The tone of this book is set by the editors' preface and the forewords. The goals of the text, stated in the first chapter, "The Philosophy of Eye Surgery," are based on the premise that excellence in surgical technique is required to reap the ultimate reward: the best uncorrected vision for the patient. The editors set out to provide understanding of the techniques necessary to

perform state-of-the-art anterior segment surgery, to provide a comprehensive reference text on the subject, and to instill in the reader the goal of achieving excellence. Excellence, they state, is characterized by five key components: universality, essential knowledge, desire, courage, and benevolence. Let us then examine the work within the framework of these characteristic components.

Universality implies that excellence may flourish within any area of human endeavor. This applies to refractive surgical skills no less than any other field.

Essential knowledge is the foundation upon which excellence is built and is certainly the basis of any good text. The information within this book is well organized, attractively formatted, and well illustrated. The chapters in Section 1, which deals with recent developments, cover a variety of topics ranging from optics to computers to perioperative anesthesia. Section 2, on surgical instrumentation, is particularly well written and contains a vast array of information about instruments, sutures, and needles used in anterior segment surgery. Sections 3 and 4 deal with surgery of the lens. These sections comprise nearly half the book. The chapters on intraocular lenses and capsulorrhexis are replete with spectacular photographs of intraocular lenses, both virgin and in situ. The chapters that follow have a dizzying array of techniques for extraction of the human lens and the approach to associated surgical complications, including ametropia. Each chapter contains an ample number of color plates depicting the steps in the procedures. The discussions are lucid and succinct. The chapters on corneal surgery deal primarily with techniques suited for refractive surgery as well as keratoplasty. The final chapters seem like afterthoughts to fill in the prerequisites for a text on anterior segment surgery. The chapter describing approaches to ptosis repair is well illustrated and well written but misplaced in a book about anterior segment surgery.

Desire to be the best is a component of excellence that should lead the reader to desire the best outcome for the patient, that is, optimal uncorrected visual acuity.

Being the best by striving for excellence brings us to courage; meaning the courage to apply the best solutions despite the previous failures. Unfortunately, the authors do not discuss the sacrifice and cost to the patient as a result of our courage and our failures. Courage may also refer to the fortitude required to pursue eradication of ametropia rather than less challenging and sight-threatening problems like cystoid macular edema or endophthalmitis.

Benevolence is the requirement that one's efforts benefit society. The authors of this book would have the reader believe that the pursuit of maximally uncorrected visual acuity should be the new paradigm for ophthalmology. In this regard, the foreword discusses the advances in cataract surgery with respect to the classical economic law of diminishing returns. The question not answered is whose returns are diminishing as our technology matures. Of course a healthy dose of rationalization never hurts the benevolence factor. The techniques described elegantly within this volume are capable of providing excellent visual function to each patient, but at what cost to the patient in terms of added risk and to society in terms of added expense?

In summary, if one can get through the propaganda presented in the introduction, this volume offers a wealth of information, presented with beautiful graphics, concerning the phacoemulsification and refractive surgery with a smattering of other techniques added for good form.

Neuro-Ophthalmology. A Practical Text. By Nancy M. Newman. Norwalk, Connecticut, Appleton & Lange, 1992. 484 pages, Index, Illustrated. $85

Reviewed by ROBERT T. SPECTOR
Iowa City, Iowa

Neuro-ophthalmology is a discipline that encompasses the entire field of medicine. Hence, no textbook on the subject can exist without certain limiting factors. In her preface, Dr. Newman states that this book is a pragmatic clinical guide to neuro-ophthalmic disorders. The book is divided into five major sections, organized in a thoughtful and coherent manner, describing anatomical findings in both systemic and local diseases of the eye. The excellent comprehensive flow charts provide the resident in ophthalmology with differential diagnoses of complaints as well as the appropriate investigative procedures to be performed in the examination. The charts take the reader through logical steps, depending on the cause of the abnormality. All the photographs and diagrams are extremely well done.

The chapters are ordered anatomically and deal with the diseases that commonly affect the eye and the visual tracts. Other sections of the book focus on headache and functional disorders, and are correlated with the affected anatomy. This book is by no means a cookbook of neuro-ophthalmology. Rather, it is a treatise that correlates the anatomy of the visual system and the clinical findings of disease.

One weakness, which might be found in any such textbook, is that the bibliography is in some areas not fully updated. This is, nonetheless, an extremely well-organized and enjoyable textbook, which contains valuable information for both the physician-in-training and the ophthalmologist interested in neuro-ophthalmology. With minor reservations, this book gets two thumbs up.

Books Received

The Changing Visual System. Maturation and Aging in the Central Nervous System. Edited by P. Bagnoli and W. Hodos. New York, Plenum Publishing Corp., 1991. 420 pages, Index, illustrated. $105

In the spring of 1991, a NATO Advanced Study Institute was held to explore changes in the visual system throughout life. This volume contains a collection of 36 papers given at that meeting and deals with morphologic and functional events in the visual nervous system such as cell induction, cell proliferation, cell migration, cell differentiation, and synaptogenesis. This is a collection for the basic scientist interested in the visual system as an experimental model for studies of early development, plasticity, and aging in the nervous system.

Corneal Alterations With Contact Lens Wear. By A. J. P. Rouwen. New York, Kugler Publications, 1992. 168 pages, Illustrated. $68

This scholarly treatise deals with the effects of contact lens wear on the cornea. Beginning with a brief introduction to contact lenses, the author then evaluates the world's literature on the clinical effects of contact lens wear on the cornea. Most of the book is devoted to the detailed description of experimental methodology and clinical studies performed by the author to investigate the use of different contact lens types in a specific test population (the military). The book focuses on early abnormalities in the cornea that might signal later complications as well as the effects of different lens types on corneal topography.

Diabetic Retinopathy. A Slide-Script Program. San Francisco, American Academy of Ophthalmology, 1992. 26 pages, illustrated. (No price given)

This slide-script program developed by the American Academy of Ophthalmology is designed for use by ophthalmologists to familiarize primary-care physicians with the types of diabetic retinopathy and their ophthalmologic management. Emphasis is on pathogenesis and clinical manifestations as well as appropriate steps in referral and care. The program is brief but includes all the salient clinical points and, as is characteristic of so many of the materials produced by the Academy, is accompanied by high-quality graphic materials. This program may also be useful in basic medical school curricula as well as for nurse practitioners and programs for physician assistants.

Medical Malpractice. Handling Ophthalmology Cases. By Sander Marc Rabin. Colorado Springs, Shepard's/McGraw-Hill, Inc., 1991. 455 pages, Index, illustrated. $99.95

This extensive treatise covers malpractice issues that occur in ophthalmology. Directed primarily to the law community, it elucidates for the legal readership those aspects of ophthalmology with which an attorney must be familiar in litigation that involves ophthalmologic care. Nonetheless, it will also be of use to any ophthalmologist who testifies as an expert witness. It provides a well-indexed, accessible source of reference information on virtually every area of ophthalmology that might come to question in the courtroom.

ABSTRACT DEPARTMENT

Edited by George B. Bartley, M.D.

Endophthalmitis following extracapsular cataract surgery. A review of 32 cases. Heaven, C. J.*, Mann, P. J., and Boase, D. L.: Br. J. Ophthalmol. 76:419, 1992.

The authors reviewed the records of 32 patients who developed endophthalmitis after extracapsular cataract surgery and in whom intraocular diagnostic taps had been performed. Among the 20 patients whose bacterial cultures were positive, gram-positive organisms were isolated in 16 (*Staphylococcus epidermidis* in 11 and *Proteus* organisms in the remaining four patients). Overall, final visual acuity of 20/200 or better was achieved in 15 of 20 eyes (75%) in the culture-positive group and 11 of 12 eyes (92%) in the culture-negative group, with a visual acuity of 20/40 or better in ten eyes (50%) and eight eyes (67%) for the two groups, respectively. The authors advocated a modified diagnostic tap in which an 18-gauge coaxial irrigation/aspiration cannula with a 0.3-mm sideport is used to obtain separate specimens from the anterior chamber and from within the capsule. A vitreous tap, intravitreal antibiotics, or vitrectomy were considered to be needed only in the presence of posterior capsular rupture or overt vitreal infection. In endophthalmitis after uncomplicated extracapsular cataract extraction in which the focus of infection is limited to the anterior segment, the authors believed that topical, subconjunctival, and systemic antibiotics are satisfactory to achieve a favorable outcome.—George B. Bartley

*Department of Ophthalmology, Queen Alexandra Hospital, Cosham, Portsmouth PO6 3LY, England.

Pterygium treated with excision and postoperative beta irradiation. Wilder, R. B.*, Buatti, J. M., Kittelson, J. M., Shimm, D. S., Harari, P. M., Rogoff, E. E., and Cassady, J. R.: Int. J. Radiat. Oncol. Biol. Phys. 23:533, 1992.

Three hundred thirty-eight patients with pterygia were treated by excision (a bare sclera technique "in most cases"), followed by beta irradiation with strontium-90 within 24 hours. Radiotherapy consisted of three weekly 800-cGy fractions in 321 of 338 patients. Fourteen patients underwent either a single 800-cGy treatment or two weekly 800-cGy treatments because they failed to return for scheduled therapy, two patients received single 1,000-cGy treatments, and one patient was treated with a single 1,800-cGy dose. Among 258 patients for whom follow-up of six months or more was available, crude local control was achieved in 225 patients (87%). The Kaplan-Meier estimate of the five-year local control rate was 84% (95% confidence interval, 79% to 89%). Improved local control was associated with the administration of three weekly 800-cGy fractions and with the initiation of radiotherapy one to eight hours after excision, as opposed to 16 to 24 hours postoperatively. Complications in 338 patients included chronic ocular irritation (17 patients), worsened vision (11 patients), telangiectasia (six patients), chronic photophobia (six patients), granuloma formation (three patients), and scleral atrophy (two patients).—George B. Bartley

*Department of Radiation Oncology, Stanford University Medical Center, Stanford, CA 94305.

An analysis of intraocular lens exchange. Lyle, W. A.*, and Jin, J.-C.: Ophthalmic Surg. 23:453, 1992.

The authors studied 101 eyes in which an intraocular lens had been exchanged. Combined procedures included penetrating keratoplasty (45 eyes), anterior vitrectomy (45 eyes), pupilloplasty (six eyes), trabeculectomy (two eyes), astigmatic keratotomy (five eyes), and lysis of peripheral anterior synechiae (six eyes). Bullous keratopathy was the most common indication for intraocular lens exchange in the eyes that concomitantly underwent penetrating keratoplasty (39 of 45 eyes [87%]). In the eyes that did not require penetrating keratoplasty, dislocation of the implant (20 of 55 eyes [36%]) and incorrect intraocular lens power (14 of 55 eyes [25%]) were the leading reasons for implant exchange. Final visual acuity was 20/40 or better in 51 eyes, and in 88 eyes the visual

acuity improved two lines or remained within one line of the preoperative level. Eyes in which an intraocular lens originally had been placed in the posterior chamber achieved visual acuity of 20/40 or better more frequently after implant exchange than eyes that originally underwent anterior chamber intraocular lens placement (P = .0001). Replacement of an intraocular lens into the posterior chamber was associated with better final visual acuity than was implantation into the anterior chamber (P = .004). Complications of intraocular lens exchange included cystoid macular edema (18 eyes), hyphema (16 eyes), glaucoma (16 eyes), posterior capsule opacification (nine eyes), and corneal graft failure (eight eyes).—George B. Bartley

*The Eye Institute of Utah, 755 East 3900 South, Salt Lake City, UT 84107.

Long-term post trabeculectomy intraocular pressures. Akafo, S. K.*, Goulstine, D. B., and Rosenthal, A. R.: Acta Ophthalmol. (Copenh) 70:312, 1992.

Eighty-one eyes on which trabeculectomy had been performed were studied. The average duration of follow-up was 9.2 years (range, seven to ten years). Of 43 eyes with chronic open-angle glaucoma, 29 (67%) maintained an average intraocular pressure below 21 mm Hg without additional therapy. Among 38 eyes with chronic angle-closure glaucoma, glaucoma from chronic uveitis, or in which trabeculectomy was combined with cataract extraction, 25 eyes (66%) required an average of 1.5 antiglaucoma medications to maintain a "normal" postoperative intraocular pressure. Cataract extraction was performed in 15 of 69 eyes (22%) at a mean of 5.1 years after the filtering procedure. Endophthalmitis developed after trabeculectomy in two eyes of the chronic open-angle glaucoma group. Goldmann visual field testing, specifically the sum of the angular extent of eight meridians 45 degrees apart as determined with comparable targets, was reported for 36 eyes. The visual field worsened in 30 eyes at rates of between 0.1% and 27% per year, whereas an improvement in the visual field was measured in six eyes.—George B. Bartley

*Department of Ophthalmology, Clinical Sciences Building, P.O. Box 65, Leicester LE2 7LX, England.

Pupillary escape. Cox, T. A.*: Neurology 42:1271, 1992.

Afferent pupillary defects usually are assessed by the alternating light test. The usefulness of the test recently has been questioned, however, and pupillary escape (redilation of the pupil during continuous illumination) has been advocated as a means of detecting unilateral or bilateral afferent pupillary defects. The author used pupillography in a simulated clinical setting to study pupillary escape in 39 normal subjects and 14 patients, including six patients with optic neuritis, four patients with anterior ischemic optic neuropathy, and one patient each with central serous retinopathy, branch retinal artery occlusion, bilateral chorioretinal degeneration, and bilateral optic neuropathy from multiple sclerosis. All of the patients had a relative afferent pupillary defect except the patient with multiple sclerosis, but only one patient had a consistent abnormality of pupillary escape, as compared to normal subjects. The author concluded that pupillary escape is an unreliable clinical technique to detect visual dysfunction. Additionally, because the amount of pupillary escape varies considerably between normal subjects and at different times in the same individual, bilateral afferent pupillary defects cannot be diagnosed with current clinical techniques. Relative afferent pupillary defects are best detected by the alternating light test.—George B. Bartley

*Department of Ophthalmology, University of Utah Health Sciences Center, 50 N. Medical Dr., Salt Lake City, UT 84132.

Migraine aura without headache. Transient ischaemic attack or not? Dennis, M.*, and Warlow, C.: J. Neurol. Neurosurg. Psychiatry 55:437, 1992.

Patients with "migraine aura without headache" can be separated from those with transient ischaemic attacks (TIA) on the basis of the onset of symptoms, which is generally gradual and which spread or intensify over minutes or hours, and from the typical migrainous nature of their visual symptoms. Fifty cases were prospectively identified and these were compared with 50 age matched patients with a TIA. Surprisingly, there were no significant differences in the prevalence of vascular risk factors and diseases in the two groups although those with

TIAs tended to have more. Only one patient with "migraine aura without headache" suffered a subsequent vascular event (a myocardial infarction). Three patients with TIAs had strokes and two others died from vascular disease. Although the results are not conclusive, they do suggest that patients with the clinical characteristics of "migraine aura without headache" have a low risk of subsequent vascular events, lower than those with TIAs, despite perhaps having similar prevalence of vascular risk factors. Although their risk factors should be treated, patients with "migraine aura without headache" should be reassured and not subjected to inappropriate and potentially hazardous investigations and treatment.—Authors' abstract

*Department of Clinical Neurosciences, Western General Hospital, Crewe Rd., Edinburgh EH4 2XU, United Kingdom.

Eye movements in myotonic dystrophy. Bollen, E.*, den Heyer, J. C., Tolsma, M. H. J., Bellari, S., Bos, J. E., and Wintzen, A. R.: Brain 115:445, 1992.

Previous studies demonstrated that eye movement smooth pursuit gain was normal in patients with myotonic dystrophy, yet the movements were interrupted by catch-up saccades. Because catch-up saccades are indicative of defective smooth pursuit, the authors analyzed smooth pursuit in ten patients with myotonic dystrophy and ten age- and sex-matched control subjects with an infrared reflection technique and software that corrected for the confounding influence of catch-up saccades. Smooth pursuit gain was decreased in the patient group. Somnolence or inattention were thought not to be responsible for this finding because the latencies of saccadic eye movements were normal. Additionally, a myopathy of the extraocular muscles was considered unlikely because of the presence of catch-up saccades and normal fixation. The authors believed that abnormalities in the periventricular white matter are a more likely explanation for the decrease in smooth pursuit gain.—George B. Bartley

*Department of Neurology, University Hospital Leiden, P.O. Box 9600, 2300 RC Leiden, The Netherlands.

Reconstruction of the third through sixth cranial nerves during cavernous sinus surgery. Sekhar, L. N.*, Lanzino, G., Sen, C. N., and Pomonis, S.: J. Neurosurg. 76:935, 1992.

The authors performed 16 reconstructive procedures on the oculomotor, trochlear, trigeminal, or abducens cranial nerves of 14 patients who underwent operations involving the cavernous sinus. In each instance the nerve either was encased by tumor (meningioma in 12 of the 14 patients) or was inadvertently injured during tumor resection. A direct end-to-end anastomosis was achieved in five nerves, whereas in the remaining 11 nerves an interpositional graft, most frequently with a portion of sural nerve, was performed. The nerves were approximated with 10-0 nylon sutures and reinforced in some instances with autologous fibrin glue. The distribution of nerve repairs was as follows: oculomotor nerve, two cases; trochlear nerve, one case; trigeminal nerve or root, four cases; abducens nerve, nine cases. Partial or complete restoration of function was achieved in 13 nerves: oculomotor nerve, two cases; trochlear nerve, one case; trigeminal nerve, three cases; abducens nerve, seven cases. Binocular vision or cosmesis was improved in those patients who had a successful recovery of cranial nerve function.—George B. Bartley

*Department of Neurosurgery, Presbyterian University Hospital, Room 9402, 230 Lothrop St., Pittsburgh, PA 15213.

Botulinum toxin treatment of supranuclear ocular motility disorders. Newman, N. J.*, and Lambert, S. R.: Neurology 42:1391, 1992.

Botulinum toxin has been shown to be useful in the treatment of strabismus from both nonparalytic and neurogenic causes. The authors treated two patients who had supranuclear disorders of presumed ischemic origin with botulinum toxin injections. The first patient had bilateral internuclear ophthalmoplegia and a left exotropia of 40 prism diopters in primary gaze. The patient was orthotropic in primary gaze within four days of injection of 2.5 units of botulinum toxin into the right lateral rectus muscle. Examination eight months after treatment showed persistent orthotropia and full versions. The second patient had skew deviation with a left hypertropia of 12 prism diopters. Diplopia resolved by the fourth day after

injection of 2.5 units of botulinum toxin into the right inferior rectus muscle. The patient was asymptomatic, orthotropic, and had full versions one year after treatment. Neither patient experienced complications from the botulinum toxin injections. The authors advised caution in using botulinum to treat patients in whom strabismus is progressive or of uncertain origin.—George B. Bartley

*Neuro-Ophthalmology Unit, Emory Eye Center, 1327 Clifton Rd. N.E., Atlanta, GA 30322.

A new variant of blepharospasm. Elston, J. S.*: J. Neurol. Neurosurg. Psychiatry 55:369, 1992.

The author described ten patients who were unable to initiate or sustain eyelid opening in the absence of overt blepharospasm. Three patients had Parkinson's disease, two patients had progressive supranuclear palsy, and five patients had no associated neurologic disease. The age range was 50 to 77 years; seven of the ten patients were men. Electromyography was performed on seven patients; three patients had an abnormal blink reflex and all seven patients demonstrated co-contraction of the levator and orbicularis muscles or an inability to sustain levator contraction. Visible or audible (by stethoscope auscultation) orbicularis contraction was documented in seven of ten patients. The author believed that the patients he studied did not have apraxia of eyelid opening but postulated rather that they had a subtype of blepharospasm that involved the pretarsal orbicularis oculi muscle. Although eight of the ten patients had been treated with botulinum toxin injections, success in maintaining eyelid opening was achieved by only two patients, both of whom also used blepharoptosis props.—George B. Bartley

*Oxford Eye Hospital, Radcliffe Infirmary, Woodstock Rd., Oxford OX2 6HE, United Kingdom.

Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. Tallstedt, L.*, Lundell, G., Tørring, O., Wallin, G., Ljunggren, J.-G., Blomgren, H., Taube, A., and the Thyroid Study Group: N. Engl. J. Med. 326:1733, 1992.

Ophthalmopathy associated with Graves' disease has been reported to develop or worsen during or after treatment for hyperthyroidism, but no previous controlled clinical trial had been performed to evaluate the effects of different antithyroid therapies on the course of ophthalmic disease. One hundred sixty-eight patients with Graves' hyperthyroidism were divided into two age groups: Group 1, 20 to 34 years (54 patients) and Group 2, 35 to 55 years (114 patients). Patients in Group 1 were randomly assigned to methimazole treatment for 18 months or to subtotal thyroidectomy, whereas patients in Group 2 were randomly assigned either of these two treatments or ^{131}I therapy. Thyroxine was administered to the patients treated with methimazole or subtotal thyroidectomy to prevent hypothyroidism, but individuals who received radioactive iodine were treated with replacement thyroid hormone only if hypothyroidism developed. Ophthalmopathy was present in 22 patients (13%) at randomization. During a minimum follow-up interval of two years, ophthalmopathy developed in 22 patients (13%) and worsened in eight patients (5%). In Group 1, the frequency of new or worsened ophthalmopathy was similar among patients treated medically (four of 27 patients [15%]) or surgically (three of 27 patients [11%]). In Group 2, eye disease developed or worsened in four of 38 patients (10%) treated with methimazole, six of 37 patients (16%) who underwent subtotal thyroidectomy, and 13 of 39 patients (33%) who received ^{131}I ($P = .02$ for the comparison between the radioactive iodine subgroup and the other subgroups combined). The risk of new or worsened ophthalmopathy was increased if the pretreatment serum triiodothyronine concentration was ≥ 5 nmol/l. The authors concluded that treatment of Graves' hyperthyroidism with ^{131}I is more likely to be followed by the development or exacerbation of ophthalmopathy than therapy with methimazole or subtotal thyroidectomy.—George B. Bartley

*Department of Ophthalmology, Huddinge University Hospital, S-141 86 Huddinge, Sweden.

Fractures of the nasolacrimal fossa and canal. A CT study of appearance, associated injuries, and significance in 25 patients. Unger, J. M.*: Am. J. Roentgenol. 158:1321, 1992.

The axial computed tomographic scans and medical records of 25 patients who sustained nasolacrimal fractures caused by motor vehicle accidents were reviewed. Thirty-six fractures of the lacrimal fossa, of the nasolacrimal canal, or

both, were identified and were classified into three types: the avulsed fragment (of the lacrimal fossa), comminuted fractures (of either the walls of the lacrimal fossa or the nasolacrimal canal), and linear fractures (of the nasolacrimal canal). Of 19 fractures that transgressed the lacrimal fossa, 15 were classified as avulsed fragments. Of 17 fractures that involved the nasolacrimal canal, 15 were comminuted and two were linear. All of the nasolacrimal fractures were associated with other facial fractures, most frequently of the complex midfacial type (20 of 25 patients). Clinical evidence of unilateral nasolacrimal obstruction was found in only five patients, three of whom underwent dacryocystorhinostomy. The author postulated that the common occurrence of an avulsion fragment helps to explain the high success rate of dacryocystorhinostomy after bony trauma: the intact lacrimal fossa protects the lacrimal sac, even if the sac is dislodged or severed from the nasolacrimal duct.—George B. Bartley

*Department of Radiology, University of Wisconsin-Madison, Medical School, E3/311 Clinical Science Center, 600 Highland Ave., Madison, WI 53792.

Malignant melanoma of the eyelid. A report of eight cases and a review of the literature. Tahery, D. P., Goldberg, R., and Moy, R. L.*: J. Am. Acad. Dermatol. 27:17, 1992.

Melanoma of the eyelid is uncommon, constituting less than 7% of head and neck melanomas. In order to identify possible prognostic indicators for survival, the authors studied the medical records of eight patients with melanoma of the eyelid who were identified among 4,301 cases of melanoma treated at their institution during a 35-year period. Additionally, descriptions of 39 patients from previous reports were reviewed. Of the 47 total patients, 25 were women. The mean age at diagnosis was 52.6 years, with a range of 14 to 80 years. The average thickness of excised melanomas was 1.91 mm. In patients in whom tumor location could be determined, involvement of the eyelid margin and conjunctiva was associated with a poorer survival than localization to the eyelid skin alone; this observation was consistent with previous reports of a worse prognosis for melanomas originating from mucous membranes, as compared with their cutaneous counterparts. The authors attributed the difference in prognosis to the delay in diagnosis for melanomas that involve the conjunctival surfaces. No conclusion was drawn concerning the appropriate width of surgical margins.—George B. Bartley

*Dermatology Consultation Suite, UCLA Medical Center, 10833 LeConte Ave., 52-121, Los Angeles, CA 90024-1750.

An acute remission of Reiter's syndrome in male patients treated with bromocriptine. Bravo, G., Zazueta, B., and Lavalle, C.*: J. Rheumatol. 19:747, 1992.

Previous animal and human investigations have suggested that the neuroendocrine peptide prolactin may play an immunomodulatory role in some autoimmune diseases, such as systemic lupus erythematosus, arthritis, iridocyclitis, and Reiter's syndrome. The authors studied the effect of bromocriptine in reducing serum prolactin levels in four male patients with Reiter's syndrome; males were chosen because their prolactin levels are lower than females and lower dosages of bromocriptine would be required. All four patients had infectious gastroenteritis, arthritis, and enthesopathy, and three of the four patients had conjunctivitis. Previous medical therapy had been unsuccessful. In two patients a marked improvement in signs and symptoms was observed 24 hours after the initiation of 2.5 mg/day of bromocriptine, whereas in the other two patients amelioration was noted four days after treatment with 5 mg/day. Remission was maintained for at least four months in all four patients while bromocriptine treatment was continued. The mechanism for bromocriptine's therapeutic effect may be by its indirect immunosuppressive effect through the blockade of pituitary and lymphocyte release of prolactin and by a concomitant decrease of lymphocyte responsiveness toward antigenic stimulation.—George B. Bartley

*Department of Rheumatology, Hospital de Especialidades, Centro Medico La Raza, IMSS. 02990, Mexico City, Mexico.

Reading skills and auditory processing ability in children with chronic otitis media in early childhood. Updike, C.*, and Thornburg, J. D.: Ann. Otol. Rhinol. Laryngol. 101:530, 1992.

The effect of recurrent middle ear disease during the first 2 years of life on auditory

perceptual skills and reading ability was examined in two groups of 6- and 7-year-old children who were pair-matched by age, gender, socioeconomic status, and receptive vocabulary. Group 1 consisted of children with documented chronic otitis media at an early age, and group 2 had no history of middle ear problems. Tests of auditory perceptual skills and reading ability were administered. Significant differences in performance on all tests of auditory processing ability and reading ability were noted.—Authors' abstract

*Department of Speech Pathology and Audiology, Ball State University, Muncie, IN 47306.

Predictors of postoperative myocardial ischemia in patients undergoing noncardiac surgery. Hollenberg, M.*, Mangano, D. T., Browner, W. S., London, M. J., Tubau, J. F., Tateo, I. M., for the Study of Perioperative Ischemia Research Group: JAMA 268:205, 1992.

A consecutive sample of 407 men at high risk for or with coronary artery disease who underwent major noncardiac operations at a Department of Veterans Affairs tertiary care hospital and who had interpretable Holter recordings was studied to identify predictors of postoperative myocardial ischemia. Five preoperative predictors were identified: (1) left ventricular hypertrophy as identified by electrocardiography; (2) a history of hypertension; (3) diabetes mellitus; (4) definite coronary artery disease; and (5) the use of digoxin. Postoperative myocardial ischemia occurred in 13 of 58 patients (22%) with no predictors, in 48 of 155 patients (31%) with one predictor, in 58 of 126 patients (46%) with two predictors, in 38 of 54 patients (70%) with three predictors, and in ten of 13 patients (77%) with four predictors. Patients who are at high risk for postoperative myocardial ischemia and who might benefit the most from intensive postoperative Holter monitoring can be identified preoperatively.—George B. Bartley

*Veterans Affairs Medical Center, 4150 Clement St. (111C3), San Francisco, CA 94121.

Measuring and managing quality of surgery. Statistical vs incidental approaches. McGuire, H. H., Jr.*, Horsley, J. S., III, Salter, D. R., and Sobel, M.: Arch. Surg. 127:733, 1992.

New rules for quality assurance provoked a comparison of effects of two approaches used concurrently for 14 years. In an incidental approach, a multidisciplinary conference reviewed all postoperative complications as they occurred and attributed each to one of six causes. Remedies were instituted and data were filed. In a statistical approach, death and complication rates were computed annually and compared with previous years' rates and with rates reported to Congress as national norms. Statistics suggested acceptable quality in each specialty but calculations were tedious and differences achieved significance too rarely or too slowly to identify problems, protect patients, and improve care. The incidental approach was popular and produced immediate improvements in patient care. Conferees attributed one half of complications to errors. Frequent acknowledgment of susceptibility to error may contribute to the safety and quality shown by our statistics.—Authors' abstract

*Veterans Affairs Medical Center, Richmond, VA 23249.

Restoration of viral immunity in immunodeficient humans by the adoptive transfer of T cell clones. Riddell, S. R.*, Watanabe, K. S., Goodrich, J. M., Li, C. R., Agha, M. E., and Greenberg, P. D.: Science 257:238, 1992.

Individuals with normal immune systems develop and maintain $CD8^+$ cytotoxic T-cell clones specific for cytomegalovirus antigen after primary infection. In patients who have undergone allogeneic bone marrow transplantation, cytomegalovirus pneumonia is a major risk until such clones are reconstituted. The adoptive transfer of antigen-specific T cells has been shown to be effective therapy for viral infections and tumors in animal models. In this study, cytomegalovirus-specific cytotoxic T cell clones were generated from three cytomegalovirus seropositive bone marrow donors, propagated in vitro for five to 12 weeks, and adoptively transferred to three major histocompatibility complex-identical bone marrow recipients. The clones were administered to the recipients by intravenous infusion weekly for four weeks in increasing cell numbers. Forty-eight hours after the first T-cell infusion, weak $CD8^+$ responses were detected in each of the three patients. Subsequent analyses showed that the adoptively transferred cytotoxic T-cell clone immunity persisted for at least one month. No toxicity from the cell transfers was detected. Possible therapeutic implications of this study include the development of $CD8^+$

cytotoxic T-cell clones specific for human immunodeficiency virus or for tumor antigens.—George B. Bartley

*Fred Hutchinson Cancer Research Center, Seattle, WA 98104.

AIDS and the conundrum of Job. Lederman, M. M.*: Am. J. Med. 92:679, 1992.

The author of this essay drew parallels between the acquired immunodeficiency syndrome epidemic and the afflictions of the biblical character Job to examine the question, "How can we reconcile suffering of the innocent with the concept of universal justice?" The tendency to distinguish "innocent" victims of the disease, such as transfusion recipients, from individuals who contract the infection by willful actions allows one simultaneously to "minimize the magnitude of the problem, show sympathy to those who 'merit' it, and still maintain a belief that there is universal justice." Similarly in the case of Job, his friends interpreted his tribulations in light of the theology of the day: suffering implies guilt and misery is an appropriate punishment for sin. Even though Job ultimately was rewarded for his faithfulness, the essayist found the conundrum unanswered because in daily life "we see that virtue and reward are not linked." He interpreted the parable of Job as providing both the gift of free will and the legitimization of compassion; we may choose to be virtuous without expecting reward and may serve the suffering without prejudging cause or guilt. The author concluded that "AIDS is not a punishment . . . our compassion and care for those who need it reflect our free choice to do the right thing, not because we have to, but for its own sake."—George B. Bartley

*Division of Infectious Diseases, Case Western Reserve University School of Medicine, 2109 Adelbert Rd., Cleveland, OH 44106.

Benedict Duddell. Pioneer oculist of the 18th century. Wyman, A. L.*: J. R. Soc. Med. 85:412, 1992.

Benedict Duddell was born around 1695 and died between 1759 and 1767. As a young general practitioner in Worksop, England, he decided to seek specialized training in diseases of the eye after he failed to save the sight of a poor man with a large, starving family. Duddell eventually studied in the busy clinic of John Thomas Woolhouse, where he "examined over a hundred blind people a day." After establishing a practice in London, he wrote his first book in 1729 in response to an earlier publication by "Chevalier" John Taylor, a flamboyant practitioner of the day who was widely regarded as a charlatan. In addition to disputing Taylor's claim of being the first to describe certain new ideas, Duddell later criticized Taylor's surgical technique after observing him operate: "Let not your eyes be dazzled. . . . Eyes were turned inside out, and Vision tossed about. . . . Operations were inconsistent with the Rules of Surgery." Of more lasting import was Duddell's description in 1729 of the posterior elastic lamina of the cornea, nearly 30 years before Descemet published his observations on the same structure. Duddell also was an early advocate of transcorneal cataract extraction, particularly if couching had failed. Although Duddell has been relegated to the status of a "scanty footnote" in some medical biographies, the author of this essay considered him to be the outstanding English ophthalmologist of the early 18th century.—George B. Bartley

*65 Nassau Rd., London SW13 9QG, England.

Of sight and song. Cogan, D. G.*: Dartmouth Medicine 16(4):34, 1992.

The author reviewed the consequences of visual loss on the careers of several well-known composers and musicians. Johann Sebastian Bach (1685–1750) had chronic ocular problems that may have been related to glaucoma, and two months before his death suffered permanent blindness after undergoing cataract-couching by John Taylor. In addition to touting Bach as one of his surgical successes, Taylor also claimed (falsely) that he had restored the sight of George Frederick Handel (1685–1759). Handel lost vision from cataracts and left £1,000 in his will to support the families of "decayed" musicians. The English composer Frederick Delius (1862–1934) contracted syphilis that eventually resulted in optic atrophy and tabes dorsalis. George Gershwin (1898–1937) developed papilledema and olfactory hallucinations from a glioblastoma multiforme; a neurosurgical procedure was attempted, but the composer never regained consciousness postoperatively. Maurice Ravel (1875–1937) also underwent an exploratory

neurosurgical operation, but no pathologic process was identified; in retrospect, his constellation of vague symptoms suggests Alzheimer's disease. Louis Braille (1809–1852) lost vision at age 3 years from a penetrating injury to one eye and probable sympathetic ophthalmia in the other eye. Braille improved, but did not invent, the reading and writing system that bears his name and also developed a system that enabled the blind to read music. Other individuals who lost vision early in life but who nevertheless flourished musically include George Shearing, Ray Charles (from glaucoma), and Tom Sullivan (from retinopathy of prematurity). The author concluded that blindness acquired in infancy "seems often to foster the creation of music-makers," whereas visual loss that occurs later in life usually severely hampers the development or expression of musical talent.—George B. Bartley

*National Eye Institute, National Institutes of Health, Building 10, Room 6C401, Bethesda, MD 20892.

Who's first on first? Goldwyn, R. M.*: Plast. Reconstr. Surg. 90:120, 1992.

"Who did what when?" This humorous and satirical editorial describes the problem of assigning priority for new knowledge and helps to explain, in part, why many journals prohibit authors from claiming to be "the first." In the author's experience, the most vitriolic battles, surprisingly, are fought over relatively minor matters, not quantum advances. "The reality is that most of us have had similar professional training, have about the same intelligence, and one person's thinking is not likely to be centuries ahead of everybody else's . . . medicine progresses by steps, more accurately by unsure creeping, and not by well-executed Nureyev leaps. While it is important to establish priority, I hope that the combatants will not destroy themselves in the process."—George B. Bartley

*1101 Beacon St., Brookline, MA 02146.

NEWS ITEMS

Send News Items to
American Journal of Ophthalmology
435 N. Michigan Ave., Suite 1415
Chicago, IL 60611

The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

Schepens International Society: Hong Kong Retina 1993

The Schepens International Society and the Chinese University of Hong Kong will cosponsor Hong Kong Retina 1993 and the 4th Meeting of the Schepens International Society March 30–April 2, 1992, in Hong Kong. For more information, write the Organizing Committee, Hong Kong Retina 1993, c/o The Hong Kong Medical Association, Duke of Windsor Social Service Bldg., 5/f, 15 Hennessy Rd., Hong Kong; telephone (852) 527-8285; fax (852) 865-0943.

Greek Intraocular Implant and Refractive Surgery Society: 7th Symposium

The Greek Intraocular Implant and Refractive Surgery Society will hold its 7th Symposium Dec. 4–6, 1992, in Athens, Greece. For additional information, write the Secretariat, 13, I. Metaxa str., 166 75 Glyphada, Greece; fax (01) 8949 045.

Instituto Barraquer de America and Sociedad Americana de Oftalmologia y Optometria: Forum in XXV Anniversario

The Instituto Barraquer de America and Sociedad Americana de Oftalmologia y Optometria will hold Forum in XXV Anniversario March 21–26, 1993, in Bogota, Colombia. For additional information, write to Forum in XXV Anniversario, Instituto Barraquer de America, Avenida 100 No. 18A-51, Bogota (8), Colombia; fax 57-1-610-4406.

Joseph F. Morgan Research Foundation: Current Trends—In Vitro, In Vivo Skin Toxicology and Eye Irritancy Testing

The Joseph F. Morgan Research Foundation will sponsor an international symposium, Current Trends—In Vitro, In Vivo Skin Toxicology and Eye Irritancy Testing, April 21–23, 1993, in Ottawa, Ontario, Canada. For further information, write Vicki Nash-Moore, Golden Planners Inc., 126 York St., Suite 401, Ottawa, ON K1N 5T5, Canada; telephone (613) 594-8226.

Universitäts-Augenklinik: Tübingen Detachment Course—Retinal and Vitreous Surgery

The Universitäts-Augenklinik will hold a course, Retinal and Vitreous Surgery, April 22 and 23, 1993, in Tübingen, Germany. For additional information, write K. Lütjens, Univ.-Augenklinik Abt. III, Schleichstr. 12, D-7400 Tübingen, Germany; fax 07071-293730.

Canadian Implant Association: Florida Winter Workshop

The Canadian Implant Association will hold its Florida Winter Workshop Dec. 27–29, 1992, at the Marriott Harbor Beach Hotel, Ft. Lauderdale, Florida. For further information, write Marvin L. Kwitko, M.D., 5591 Côte des Neiges Rd., Ste. 1, Montreal, Quebec, Canada H3T 1Y8; telephone (514) 735-1133; fax (514) 731-0651.

Manhattan Eye, Ear & Throat Hospital: International Symposium on Indocyanine Green Angiography

The Department of Ophthalmology of the Manhattan Eye, Ear & Throat Hospital will sponsor International Symposium on Indocyanine Green Angiography Jan. 15 and 16, 1993, in New York City. For further information, write Kimberly Corbin, Dept. of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3760; fax (212) 753-7699.

New England Eye Center: Innovations in Clinical Ophthalmology—1993

The New England Eye Center will sponsor Innovations in Clinical Ophthalmology—1993

Jan. 25–29, 1993, at the Grand Hyatt Wailea Resort and Spa, Maui, Hawaii. For additional information, write Mark E. Keller, M.D., New England Eye Center, 750 Washington St., Box 450, Boston, MA 02111; telephone (617) 956-4261.

New York Society for Clinical Ophthalmology: Fall Meeting

The New York Society for Clinical Ophthalmology will hold its Fall Meeting Oct. 24, 1992, in New York City. For more information, write Francine Leinhardt, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 838-9200 ext. 2776; fax (212) 832-9126.

University of North Carolina: Ophthalmology Residents' Day

The Department of Ophthalmology at the University of North Carolina at Chapel Hill will have the annual Ophthalmology Residents' Day Dec. 5, 1992. For further information, write Mrs. Christine C. Cotton, Dept. of Ophthalmology, CB7040, 617 Burnett-Womack Bldg., University of North Carolina, Chapel Hill, NC 27599-7040; telephone (919) 966-5296.

Wilmer Ophthalmological Institute: 15th Annual Current Concepts in Ophthalmology

The Wilmer Ophthalmological Institute of the Johns Hopkins Medical Institutions will sponsor its 15th Annual Current Concepts in Ophthalmology with phacoemulsification wet lab and vitrectomy workshop for the anterior segment surgeon Feb. 7–12, 1993. For further information, write the Program Coordinator, Johns Hopkins Medical Institutions, Office of CME, Turner Bldg., 720 Rutland Ave., Baltimore, MD 21205-2195; telephone (410) 955-2959.

Ronald G. Michels Fellowship Foundation: Annual Fellowship Awards

The Ronald G. Michels Fellowship Foundation makes an annual award to a first-year or second-year fellow or to a resident who has been accepted in a vitreoretinal surgery training program. The candidates are judged by a Selection Committee on a competitive basis. The annual deadline for submission of applications is July 1. For further information, write Mrs. Ruth E. Classon, Ronald G. Michels Fellowship Foundation, P.O. Box 9898, Baltimore, MD 21284-9898; telephone (301) 337-4500; fax (301) 337-3975.

Chicago Ophthalmological Society: 1992-1993 Officers

The Chicago Ophthalmological Society has elected the following officers for 1992-1993: Elise Torczynski, president; Thomas Deutsch, vice president; Allen Putterman, president-elect; Alan Axelrod, secretary/treasurer; Robert Schroeder, corresponding secretary; Samir Patel, monthly program chairman; James Kapustiak, conference chairman; and Paul Morimoto, councilor.

Eye-Bank for Sight Restoration: Medical Advisory Board Members and Officers Elected

The Eye-Bank for Sight Restoration has elected Robert D'Amico as secretary of its Medical Board. The following three new regular members were also elected to the Advisory Board: George Florakis, David Haight, and Mitsugu Shimmyo.

Personals

John E. Dowling

John E. Dowling was awarded the 1992 von Sallmann Prize in Vision and Ophthalmology. Dr. Dowling is professor at Harvard University in Cambridge, Massachusetts. The prize was awarded at the 10th Congress of Eye Research in Stresa, Italy, Sept. 16–26, 1992.

Dunbar Hoskins

Dunbar Hoskins of San Francisco has been named executive vice president of the American Academy of Ophthalmology, succeeding Bruce E. Spivey.

Community Care of Corneal Ulcers

Peter J. McDonnell, M.D., Janis Nobe, M.D., W. James Gauderman, Ph.D., Paul Lee, M.D., Amy Aiello, M.D., and Melvin Trousdale, Ph.D.

Because of increasing concern about the appropriate and cost-effective use of eye care services and procedures, several organizations have sought to arrive at practice guidelines or practice patterns from which physicians can draw guidance. To assess the potential effectiveness of such guidelines, we reviewed the care of patients with corneal ulcers. Corneal specialists recommend that cultures be obtained before initiation of treatment. We determined whether ophthalmologists implemented these guidelines by the following: (1) a review of records of 79 patients referred to a tertiary care corneal and external disease service for evaluation of keratitis, and (2) a survey by mail of practicing ophthalmologists. Antibiotic therapy without any cultures was observed in 38 of 79 referred patients with corneal ulcers (48.1%). Our survey of general ophthalmologists disclosed that 274 of 560 patients with corneal ulcers (48.7%) were treated with antibiotics without any cultures being obtained. Compliance with recommended practice in the care of corneal ulcers is poor, as measured with either method. This procedure provides insights into more effective implementation of future practice guidelines.

In the evaluation of possible microbial keratitis, both corneal specialists and nonspecialists recommend microbiologic examination, including corneal scraping for smears and cultures, and treatment with fortified antibiotics.[1-5] Despite this uniformity of published opinion regarding the evaluation of possible microbial keratitis, it has been our impression that of the patients referred to our tertiary care practice because of corneal ulcers, many had been treated with antibiotics without previous scrapings and cultures. Accordingly, we sought to determine the prevailing practice among ophthalmologists in our geographic area, Southern California, and the possible explanations for any discrepancy with published recommendations.

See also p. 630.

The care of corneal ulcers was chosen to investigate the issue of physician compliance with recommended practice patterns because of the uniformity of expert opinion. Unlike other areas of ophthalmology in which there has been disagreement in the literature (for example, the role of corticosteroids in the treatment of optic neuritis, and the appropriate time of surgical intervention in the treatment of glaucoma), there is uniform agreement that cultures should be performed in cases of suspected microbial keratitis. Whether this is a cost-effective approach, or is associated with the best possible outcome, was not the subject of this study. Rather, we wished to determine how well physicians follow this recommended pattern of care.

Material and Methods

Chart review—The records of all patients with corneal ulcers admitted to the Estelle Doheny Eye Hospital between April 1, 1988, and Sept. 30, 1989, were reviewed. During this time, we admitted all referred patients with suspected microbial keratitis for around-the-clock treatment with fortified antibiotics. These patients were referred specifically to one of

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From the Doheny Eye Institute, and Department of Ophthalmology, University of Southern California School of Medicine, Los Angeles, California. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York, New York; and by Core Grant EY03040 from the National Eye Institute. Dr. Nobe was a 1990–1991 Heed Ophthalmic Fellow and Dr. Lee was a 1990–1991 Heed Ophthalmic Fellow.

Reprint requests to Peter J. McDonnell, M.D., Doheny Eye Institute, 1450 San Pablo St., Los Angeles, CA 90033.

three corneal and external disease fellowship-trained specialists whose practices consist solely of tertiary care referrals from ophthalmologists. To evaluate the treatment pattern of these corneal ulcers, we questioned the referring physician and the patient to determine whether the patient was using antibiotics at the time of referral and whether cultures had been performed by the referring physician before instituting therapy. Patients taking antibiotics were asked to produce the bottles at the time of referral. All patients, whether already treated with antibiotics, had cultures of their corneal ulcers performed at our institution by a physician who used a Kimura spatula to scrape the leading edge of the ulcer; the collected material was immediately plated on culture media (blood and chocolate agar, thioglycolate medium, Sabouraud dextrose agar, and, at the discretion of the clinician, Lowenstein-Jensen medium [for *Mycobacterium* organisms] and nonnutrient agar with *Escherichia coli* overlay [for *Acanthamoeba* organisms]). The results of these cultures were tabulated in our survey. All patients were hospitalized for therapy with fortified antibiotics; this therapy was modified, as necessary, in accordance with the results of cultures and sensitivity determinations.

As a measure of the severity of the corneal ulcers in these referred patients, we noted the dimensions of the stromal infiltrates; as a measure of healing rates, we used the time required for complete re-epithelialization of the cornea.

Survey of practicing ophthalmologists—To determine the practice patterns of ophthalmologists in our geographic region, and to compare these patterns with the data generated from analyzing the population of referred patients, a questionnaire was developed and mailed to a sample of ophthalmologists in Southern California. The following questions were included in the questionnaire:

1. In the last 12 months, how many corneal ulcers have you seen in your practice?
2. What percent of these ulcers were immediately referred to a corneal specialist and what percent did you treat?
3. Of those you treated, what percent were cultured with a cotton swab, with a metal spatula (that is, scraped), and what percent had Gram stains performed?
4. Of those ulcers you treated, what percent did you refer to a corneal specialist because they worsened or failed to improve despite therapy?
5. In your office, do you have culture media, transport media, or Gram-stain material?
6. In your opinion, scrapings for Gram stain and culture are (circle one): always necessary, necessary only for large or severe ulcers, unnecessary, or other (specify).
7. What is (are) your antibiotic(s) of choice for the initial management of corneal ulcers?
8. How many of these ulcers were previously treated by a nonophthalmologist physician before seeing you?

We also requested that the physicians enter the five-digit zip code of their offices on the returned questionnaire so that we could assess whether variations in practice patterns correlated with the economic level of the community in which the practices were located. To select ophthalmologists who would receive the questionnaire, an alphabetical listing of all practicing general ophthalmologists in Los Angeles and Ventura counties of Southern California was used; a questionnaire was sent to every sixth ophthalmologist on this list. A total of 114 ophthalmologists were identified. A confidential questionnaire and stamped, addressed return envelope were mailed to each.

Statistical methods—Chi-square tests, two-sample *t*-tests, and Spearman nonparametric correlation coefficients were used to investigate associations of interest. For responding physicians whose practices were in Los Angeles County (45 ophthalmologists), the median family income in the zip code–defined area of their practice was calculated by using 1980 census data.[6] All statistical tests were performed using a two-sided, .05 significance level. Data were reported as mean ± standard deviation.

Determination of costs associated with microbiologic studies—A telephone survey was made of commercial medical laboratories in Southern California to determine the fees charged for bacterial and fungal cultures and for antibiotic sensitivities. We contacted three national manufacturers of culture media to determine the costs associated with purchase and in-office storage of culture media (blood agar, chocolate agar, and thioglycolate medium).

Results

Review of referred patients with corneal ulcers—Of the 79 patients with ulcers referred to us and subsequently admitted for antibiotic

therapy and observation, 64 (81%) had not had corneal ulcers previously cultured and 15 (19%) had corneal ulcers cultured by the primary ophthalmologist. Of the 64 patients who had not had cultures, 38 (59%) were using one or more antibiotics, and the remaining 26 (41%) were referred before treatment. Cultures were performed on all 79 patients on referral to our institution. We recovered organisms from 23 of the 38 ulcers (60.5%) that were treated by the referring physician with antibiotics but not cultured before treatment. Of the 26 patients referred without previous treatment, 19 (73%) had positive cultures; although positive cultures were more common in eyes not treated with antibiotics, the difference between the two groups was not statistically significant ($P = .30$).

The interval between initial examination and referral to the corneal specialist at our institution was shorter for those patients not empirically treated by the referring doctor (0.50 ± 0.25 day) than for those patients in whom therapy was initiated by the referring ophthalmologist and subsequently referred (3.2 ± 2.8 days) ($P = .003$). In the 74 patients referred for treatment of corneal ulcers, the measured infiltrate size was 17.4 ± 2.5 mm^2 in patients who were being treated with antibiotics at referral compared to 8.9 ± 2.6 mm^2 for the 23 patients not being treated with antibiotics at referral. The time required for complete epithelial healing was 24.5 ± 3.8 days for eyes previously treated with antibiotics and 15.8 ± 2.6 days for eyes not previously treated with antibiotics. Patients who were being treated with antibiotics at the time of referral had larger corneal infiltrates, on average, than did those not being treated with antibiotics ($P = .042$), and complete resolution of the epithelial defect required an average of nine days longer ($P = .176$).

Survey of ophthalmologists—Responses were received from 64 of the 114 ophthalmologists (56.1%) to whom a questionnaire was mailed. One respondent was a retinal specialist; to the best of our knowledge all of the other respondents were general ophthalmologists, and none were corneal and external disease experts. These 64 physicians reported that they had seen a total of 627 patients with corneal ulcers in their practices during the previous 12-month period (mean ± standard deviation = 9.8 ± 9.3 cases per physician; range, zero to 50 cases). Most ophthalmologists reported seeing about one patient with a corneal ulcer per month. Only two ophthalmologists reported seeing more than 20 patients with ulcers in a 12-month period, and only one ophthalmologist estimated seeing 50 patients with ulcers in a 12-month period. Of these 627 patients, 67 (10.7%) were immediately referred to a specialist in corneal and external diseases; the remainder (560 patients) were treated by the primary ophthalmologist. Of the 560 corneal ulcers treated by the primary ophthalmologist, 175 (31.3%) were cultured with a cotton-tipped applicator and 111 (19.8%) were scraped with a metal instrument for culture. Treatment with antibiotics was initiated in almost one half (274; 48.9%) of the patients without any previous cultures.

Scraping for a Gram stain was performed in 98 of 560 patients (17.5%). Only 81 of 560 ulcers (14.5%) were scraped for both culture and Gram stain.

The respondents (61 ophthalmologists; three did not respond to this question) rated the necessity of scrapings for Gram stain and culture as follows: always necessary (14 ophthalmologists; 23.0%), necessary only for large or severe ulcers (35 ophthalmologists; 57.3%), unnecessary (two ophthalmologists; 3.3%), or other (ten ophthalmologists; 16.4%). Specific responses in the "other" category included the following: reserved for large central ulcers (two respondents), only if the diagnosis is in doubt (one respondent), only if initial therapy is unsuccessful (two respondents), clinical judgment (two respondents), usually necessary (one respondent), and depends on size and history (two respondents). Of the 64 respondents, 14 (21.8%) had culture media, 37 (57.8%) had transport media, and six (9.4%) had material for Gram staining in their offices or immediately available. The performance of cultures was not significantly correlated with the number of corneal ulcers seen by the respondents.

Responding physicians indicated their antibiotics of choice for the initial treatment of corneal ulcers (Table). The most popular choice was an aminoglycoside (tobramycin or gentamicin, listed by 42 of 64 respondents [65.6%] and 28 of 64 respondents [43.8%], respectively). Fortified antibiotics were specified by nine of 64 respondents (14.1%), collagen shields by three of 64 respondents (4.9%), and subconjunctival administration by three of 64 respondents (4.9%). Four of 64 respondents (6.2%) used topical corticosteroids as part of the initial therapy of ulcers.

TABLE
ANTIBIOTICS USED IN THE INITIAL TREATMENT OF CORNEAL ULCERS

ANTIBIOTICS	RESPONDENTS* NO. %
Tobramycin	42 (65.6)
Gentamicin	28 (43.8)
Cefazolin	9 (14.1)
Polymyxin B, bacitracin, and neomycin	8 (12.5)
Bacitracin	5 (7.8)
Trimethoprim and polymyxin B	4 (6.2)
Sulfacetamide	3 (4.9)
Polymyxin B and bacitracin	2 (3.2)
Chloramphenicol	2 (3.2)
Polymyxin B	1 (1.6)

*Exceeds 100 because some physicians used more than one antibiotic.

The strategy of antibiotic therapy without previous cultures (used in 274 of 560 patients [48.9%]) or after culture with only a cotton-tipped applicator (used in 175 of 560 patients [31.3%]) seemed to be reasonably effective according to the survey. Of the total number of 560 patients treated by the primary ophthalmologists, only 35 (6.3%) were subsequently referred to a specialist in corneal and external disease because of worsening or no improvement. For the subset of physicians who responded that they performed cultures in either none of their patients who had corneal ulcers or all of their patients with ulcers, we tabulated the corresponding number of patients who had to be referred to a corneal specialist because of worsening or no improvement in the ulcer despite antibiotic therapy. From this subset, 148 ulcers were not cultured, but only three (2%) did not heal and were referred to a corneal specialist. Of 162 patients whose ulcers were cultured with a metal spatula or cotton-tipped applicator, 17 (10.5%) reportedly required subsequent referral to a specialist ($P < .01$, compared with the group in whom no cultures were performed).

Our survey disclosed that 19 of 64 ophthalmologists (30%) used one antibiotic for empiric therapy and 45 of 64 (70%) used two or more. For the subset that used one antibiotic, 11 of 128 patients (8.6%) required subsequent referral to a corneal specialist, while for those ophthalmologists who used more than one antibiotic, 24 of 432 patients (5.6%) were referred to a specialist. The difference between the two groups was not statistically significant ($P = .21$).

We sought to determine whether the likelihood of a corneal ulcer being cultured depended on the relative affluence of a community. We found a weak but statistically significant positive correlation ($r = .37$; $P = .02$) between median family income and the proportion of patients whose ulcers were cultured with a metal spatula. No correlation was found, however, between median family income and the proportion cultured with a cotton swab ($r = .06$; $P = .71$).

Our survey disclosed that 92 of the 560 patients (16.4%) cared for by the ophthalmologists who answered our questionnaire had been treated previously by another physician who was not an ophthalmologist.

Costs associated with in-office maintenance of equipment for corneal scraping for Gram stain and required culture supplies during the course of a year were determined. These costs included $363.60 for culture media (blood and chocolate agar, thioglycolate, and the like), $36.20 for two Gram stain kits, $128.60 for two Giemsa stain kits, $28.24 for two boxes of glass slides, $100.00 for a Kimura spatula, $4.60 for an alcohol lamp, and $79.51 for a case of cotton-tipped sterile applicators. This total cost is $740.75. This takes into account the need to replace culture media as they expire during the 12-month period. The fee charged by laboratories in Southern California to identify an isolate was about $50 per culture, and the fee for antibiotic sensitivity testing ranged from $30 to $55 per isolate.

Discussion

Despite an extensive and uniform literature describing the necessity of and technique for extensive microbiologic evaluation of suspected microbial keratitis, many ophthalmologists in our region of the country apparently do not follow these recommendations. The review of our referrals and the questionnaire indicated that many ophthalmologists do not culture every corneal ulcer before instituting antibiotic therapy. Of those ulcers that are cultured, the technique used in most instances does not conform with published recommendations[1-5]; cotton-tipped applicators and transport media are

generally used instead of metal spatulas and direct inoculation of media. Only about 10% of ophthalmologists had material for Gram stain in their offices or immediately available to them, and only 14.5% of ulcers were examined with scraping for both Gram stain and cultures, the approach recommended in all standard texts on the subject.

We found a dramatic discrepancy between published recommendations and actual practices. One possible reason for the discrepancy is that currently available antibiotics are so effective that treatment failures, even when a specific causative organism is not identified, are uncommon. According to our survey, about one half of the patients with corneal ulcers are treated without any laboratory examination, and in only about 35 of 560 (6.3%) do the ulcers fail to heal, necessitating referral to a specialist. A recent study suggested that 96% of culture isolates from community-acquired corneal ulcers are effectively treated with both aminoglycoside and cephalosporin drops on initial examination.[7]

In our chart review, we identified 38 patients who were referred after apparent failure of antibiotic therapy that had been instituted without previous culture. Our survey suggested that this number represents only a small fraction of the total number of ulcers treated empirically, without microbiologic examination. Some clinicians may conclude that a given success rate (such as greater than 90%) with ulcer treatment without cultures may not justify the expense and time involved with microbiologic studies.

Another possible explanation for nonreliance on cultures in our region might be the rather common failure of cultures to identify a pathogen. In one study limited to cases of contact lens–related corneal ulcers seen at six university ophthalmic centers by corneal specialists and determined to have ulcerative keratitis (corneal epithelial defect with underlying stromal infiltrate), cultures of corneal scrapings were positive in only 63% of patients.[8] Other reports similarly indicate that many cases of ulcerative keratitis, presumed to be microbial, yield negative cultures[9-19]; in our own group of 26 corneal ulcers, thought by us to be microbial in origin and not already treated with antibiotics, a positive culture was obtained in only 19 (73%). Physicians who have only cotton-tipped applicators and transport media available may encounter a positive culture rate substantially lower than those in the previously mentioned studies, which could well lead some to doubt the value of and to eventually abandon the use of in-office cultures.

Physician time and the expense associated with microbiologic examination of patients with ulcers may be another consideration. Perhaps ophthalmologists would be more likely to perform microbiologic studies in relatively affluent areas, in which patients might have more complete insurance coverage or be personally better able to pay for these studies. In this regard, we did find a weak, but statistically significant positive correlation between median family income within the zip codes of responding ophthalmologists and the likelihood of their scraping corneal ulcers with a metal spatula. No correlation was present between income and likelihood of culture with a cotton-tipped applicator. The average ophthalmologist responding to our survey saw about ten patients with corneal ulcers per year. The cost associated with maintaining the equipment necessary for the recommended laboratory studies would be about $740, or about $74 per corneal ulcer, not including the expense associated with purchase and maintenance of a microscope for examination of smears. We conducted a telephone survey of the fees charged by microbiologic laboratories in Southern California for bacterial and fungal identification and sensitivities, and found these fees to average about $90 per isolate, for a total expense of about $163 per corneal ulcer. One factor considered by the many ophthalmologists who do not routinely culture corneal ulcers might therefore be the cost associated with these cultures. A recent study found that knowledge of the costs of laboratory procedures and tests at the time that they are ordered reduces the frequency of such orders.[20] At a time of heightened cost awareness, this supports the idea that some ophthalmologists may not routinely culture ulcers because of the costs involved. We can roughly calculate, on the basis of our survey of about 1/12 of the ophthalmologists in our area, that about 7,200 (600 × 12) corneal ulcers are seen annually in our region of the country alone; cultures of all of these ulcers would cost 7,200 × $163, or about $1,173,600 per year. Against this must be weighed the costs of prolonged therapy, possible hospitalization, and lost wages and productivity when ulcers that are not cultured and are treated with inappropriate antibiotic therapy progress.

We believe the data generated by this study are of potential medicolegal importance. In the absence of data such as were generated by our survey, it might seem logical to refer to the practices described in standard texts[1-5] as reflecting the current standard of care. Our data suggest, however, that it would not be appropriate to equate these written guidelines with the actual practice of most practicing ophthalmologists in our community, as these written guidelines (scraping the ulcer for Gram stain and culture) are complied with in only 81 of 560 treatments of ulcers (14.5%). Although we did not question respondents about the performance of eyelid and conjunctival cultures, we suspect that even fewer comply with this recommendation.

Although not a primary focus of our study, we can examine our data for a demonstrable advantage to complete microbiologic examination of ulcers with immediate plating of material scraped off the surface of the cornea with a metal spatula. In our review of referred patients with corneal ulcers, those patients who were not being treated with antibiotics, and whose ulcers were immediately scraped and cultured and treated with fortified antibiotics by us had smaller infiltrates at the time of referral ($P = .042$) and healed, on average, almost nine days sooner than did the ulcers of patients who were being treated with antibiotics at the time of referral. However, the difference between healing times was not statistically significant. If it is correct to assume that these antibiotic-treated ulcers were more advanced because the antibiotics used were not effective against the organism or were not sufficiently concentrated, these data would suggest that the course of the disease was prolonged and the outcome was possibly worsened by antibiotic therapy without previous complete microbiologic examination.

The poor compliance with the recommended practice pattern in these patients with corneal ulcers may reflect many different factors and concerns. Factors identified in other studies suggest that other reasons may also be important. With regard to corneal ulcers, concerns with practitioners' unfamiliarity with published recommendations, unclear or poorly understood recommendations, or patient refusal clearly do not apply.[21-23] However, poor reimbursement, insufficient time, logistic barriers, or practitioner skepticism about published recommendations may be important.[24-27] These concerns raise at least two fundamental issues.

The first is whether noncompliance with the guideline reflects a widespread belief among general ophthalmologists that the practice pattern being recommended is inappropriate. If this is the case, then the need to use methods of guideline development that allow modification of practice patterns is important. Because most current guidelines incorporate expert panel involvement, a need for a more diverse range of physician involvement in such panels may be indicated, as in the American Academy of Ophthalmology's preferred practice pattern development process. Data from at least one study, alluded to previously, suggest that empiric combination therapy may be effective in more than 96% of cases with cultured organisms. This may result in further physician skepticism of the need for mandatory cultures. Clearly, more definitive data on outcomes would be helpful in addressing these questions.

The second important issue concerns possible approaches to increasing physician compliance with the recommended practice patterns if such patterns are appropriate. Education programs directed to physicians may be effective.[28] Additionally, imposition of medicolegal factors may influence physician response. While this remains an unsettled issue, legal commentary on the implications of formal practice patterns suggests that such patterns would not be conclusive in most instances, but might provide strong evidence in any malpractice proceeding.[28] Additional investigation is needed to determine the relative importance of factors such as time constraints, reimbursement shortfalls, and logistic barriers in this process.

Our study has several potential limitations. The survey we performed, for practical reasons, was a random sampling of practicing ophthalmologists, and thus did not include every practicing ophthalmologist in our region; we do not know whether the 64 of 114 ophthalmologists who responded to our survey (56.1%) differed from the nonrespondents in terms of corneal ulcer treatment. We would expect, however, that respondents would be more likely to respond if they had favorable outcomes with their therapeutic choice or if their practices were in accord with published suggestions. As such, the study may well underestimate the rate of treatment without culture that actually exists.

We also do not know, out of the total number of patients, how many might have represented peripheral possibly noninfectious subepithelial infiltrates (perhaps with only mild epithelial disruption) or other similar conditions rather than typical central or paracentral ulcers with

infiltrates or necrosis, or both. This limitation is similar to that of other studies of microbial keratitis that have relied on surveys of physicians.[8,19] For the purposes of this study, however, this is less of a concern, since our study focused on physician compliance with recommended guidelines. It is sufficient to note that the practicing physician believed the lesion being treated to be a corneal ulcer. As such, under the recommended guidelines, cultures should have been obtained before initiating antibiotic therapy.

It would be useful to know whether other tertiary care institutions share our experience of having a high percentage of referred patients with corneal ulcers treated with antibiotics without previous cultures. Poggio and associates[19] refer to a similar phenomenon in a survey in which "telephone inquiries to ophthalmologists confirmed a high rate of empirical treatment without culture," although they do not quantify this observation. Their study, performed in New England, suggests that our analysis of corneal ulcer treatment in Southern California might be valid in other regions of the country as well. An important limitation of our study is the lack of long-term clinical outcome, specifically in terms of ultimate visual acuity or eventual need for keratoplasty. Almost all the 79 patients in our study were returned to the care of the referring ophthalmologist once the corneal ulcer was healed, so that long-term follow-up data are not available.

Most ophthalmologists in our study saw one ulcer or less per month. Only two ophthalmologists saw more than 20 ulcers in a 12-month period, and one ophthalmologist saw 50 ulcers. Because contact-lens wear is a well-known risk factor for development of corneal ulcers, one possibility might be that ophthalmologists with large contact-lens practices would tend to see more ulcers than ophthalmologists without such contact-lens practices.

Our study was not designed to determine the most appropriate treatment of corneal ulcers. Carefully performed large studies examining different corneal ulcer treatment strategies and comparing patient outcomes are lacking. Because we occasionally see ulcers caused by resistant organisms, requiring timely modification of antibiotic therapy, we perform complete microbiologic examination of all ulcers at the time of initial examination at our institution. We teach our resident staff to do the same, and include such teaching in our continuing medical education program.

As is true in all of medicine, deciding on a set of guidelines or an effective treatment has less meaning without a program to ensure adequate implementation of such practices. Although practice patterns and guidelines have tremendous potential and promise to improve the quality of care, our study suggests that the implementation of such guidelines in ophthalmology, as elsewhere in medicine, poses a challenge in the years to come. Implementation might be made difficult because of disagreement about the appropriateness of the guidelines or for several other reasons not yet clear. Additional study and effort will be needed so that practice patterns will evolve into widely accepted and implemented vehicles for improving the care of our patients.

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Lattice Degeneration of the Retina and the Pigment Dispersion Syndrome

Peter Weseley, M.D., Jeffrey Liebmann, M.D., Joseph B. Walsh, M.D., and Robert Ritch, M.D.

Retinal detachment occurs more frequently in patients with pigment dispersion syndrome. We evaluated the incidence of peripheral retinal abnormalities known to predispose to rhegmatogenous retinal detachment in a consecutive series of 60 patients with pigment dispersion syndrome with or without glaucoma. Lattice degeneration was present in at least one eye of 12 patients (20%). Seven patients had bilateral lesions. Full-thickness retinal breaks were found in seven patients (11.7%) and two patients (3.3%) had asymptomatic rhegmatogenous retinal detachments that required scleral buckle procedures. The incidence of lattice degeneration and full-thickness retinal breaks appears to be increased in this group of patients, and may be responsible for the increased risk of rhegmatogenous detachment.

THE PIGMENT DISPERSION SYNDROME is characterized by the liberation of pigment from the iris pigment epithelium and its deposition on the structures of the anterior segment. Clinical features include increased trabecular meshwork pigmentation, Krukenberg spindles, and midperipheral, radial, slitlike iris transillumination defects.[1,2] Eyes with pigment dispersion syndrome are predisposed to develop glaucoma[2] and are usually myopic.[2,3] The syndrome appears to be inherited as an autosomal dominant trait.[4,5] Patients with pigment dispersion and pigmentary glaucoma have an increased risk of retinal detachment.[2,6] The reason for this apparent association is unknown.

We prospectively analyzed data from a series of consecutive patients with pigment dispersion syndrome or pigmentary glaucoma to determine if retinal lesions known to predispose to rhegmatogenous retinal detachment occur at a higher rate in these patients than in the general population.

Patients and Methods

We enrolled all patients who were examined at the Glaucoma Service at the New York Eye and Ear Infirmary between June 1, 1990, and May 31, 1991, who had a diagnosis of pigmentary glaucoma or pigment dispersion syndrome. The diagnosis was confirmed by two of us (R.R., J.L.) and required that the following three findings be present: Krukenberg spindles; increased trabecular meshwork pigmentation; and characteristic midperipheral, slitlike iris transillumination defects. Patients with other ocular disease known to cause any of these findings were excluded. Two of us (J.B.W., P.W.) examined the fundi of each patient. Any patient referred for examination of retinal disease was excluded.

The pupils of all patients were dilated with tropicamide 1% and phenylephrine 2.5% and were examined by indirect ophthalmoscopy with scleral depression. The criteria for the diagnosis of lattice degeneration have been described elsewhere.[7-9] All of the lesions that we classified as lattice degeneration were located at or anterior to the equator, were oval or cigar shaped with their long axes parallel to the ora serrata, and were sharply demarcated by a sudden discontinuity in the otherwise smooth retinal surface. Other findings such as white lines or pigment clumping were variably pres-

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From the Department of Ophthalmology, New York Eye and Ear Infirmary, New York, New York; and Department of Ophthalmology, New York Medical College, Valhalla, New York. This study was supported by The Glaucoma Foundation, New York, New York. This study was presented in part at the annual meeting of the Association for Research in Vision and Ophthalmology, Sarasota, Florida, May 3, 1992.

Reprint requests to Jeffrey M. Liebmann, M.D., Department of Ophthalmology, New York Eye and Ear Infirmary, 310 E. 14th St., New York, NY 10003.

ent. If the nature of any lesion was in doubt, the patient was also examined with a Goldmann contact lens. Data were collected with regard to age, gender, race, refractive error, history of ocular trauma or surgery, and ophthalmic drug use.

The prevalences of lattice degeneration for the whole group and for subgroups defined by refractive error were then calculated. The data were then compared to data derived from a group of patients described by Byer.[8] The data in the literature were represented by a bar graph that illustrated the distribution of refractive errors in a group of eyes in which lattice degeneration was found and in the group of eyes that were screened to find the eyes with lattice degeneration. The data were converted to numerical form and prevalence data were calculated. Statistical analysis used the Mantel-Haenszel chi-square statistic[10] to test for differences between the prevalence of eyes with lattice degeneration in the study population and the prevalence of eyes with lattice degeneration in Byer's population while controlling for levels of refractive error. This statistical technique also permitted calculation of a summary chi-square test and a summary odds ratio (approximately equal to the relative risk) adjusted for differences in the distributions of refractive errors.

Results

Sixty patients were enrolled. One patient was monocular. Nineteen were women and 41 were men. No patients were related. The mean age was 44.9 ± 12.3 years (range, 26 to 78 years). Fifty-seven patients were white and three were Hispanic. The mean refractive error was −4.2 ± 3.1 diopters (range, +0.75 to −13.25 diopters). Axial lengths were obtained on 81 eyes of 41 patients. The mean axial length of these eyes was 25.1 ± 1.4 mm (range, 22.3 to 29.5 mm).

Nineteen of 119 eyes (15.9%) (12 of 60 patients [20%]) showed lattice degeneration of the retina. Four of these patients were women and eight were men. The mean refractive error in eyes in which lattice lesions were found was −4.8 ± 3.5 diopters (range, −1.00 to −12.75 diopters) as compared to −4.1 ± 3.1 diopters (range, +0.75 to −13.25 diopters) in eyes without lattice lesions (not significant). The mean axial length of the eyes that had been measured and that had lattice lesions was 25.3 ± 1.3 mm (range, 22.7 to 26.7 mm) vs 24.7 ± 3.1 mm (range, 22.3 to 29.3 mm) in eyes without lattice lesions (not significant). Miotic therapy had been used in seven of 19 eyes (37%) with lattice lesions as compared to 62 of 119 eyes (52%) that had been examined.

The prevalence of lattice degeneration in our patients was greater than that found by Byer[8] for all degrees of myopia (Table). The summary odds ratio adjusted for refractive error for lattice degeneration in pigment dispersion syndrome vs lattice degeneration in the general population was 2.68 (95% confidence interval, 1.45; 5.01), which was significant ($P < .001$).

Seven of 60 patients (11.7%) had retinal breaks. Horseshoe-shaped tears were present in three eyes, two of which occurred in eyes without lattice lesions. Atrophic round holes were found in four eyes and three of the holes were located in lattice lesions. The three eyes with horseshoe-shaped tears had never been treated with miotic agents. Two of the four eyes with atrophic holes had been treated with pilocarpine (Ocusert, Alza Corporation, Palo Alto, California). Fifteen of 60 patients (25%) had at least one break or lattice lesion in at least one eye.

Two of 60 patients (3.3%) had rhegmatogenous retinal detachments. The causative break in one case was an atrophic hole in a lattice lesion in a 36-year-old man with a refractive error of −3.00 diopters in whom pilocarpine (Ocusert) therapy had been initiated two months previously. He had no symptoms to suggest a retinal detachment. The second detachment was associated with an asymptomatic horseshoe-shaped tear at the edge of a lattice lesion in a 33-year-old woman with a −12.75-diopter refractive error who had never used miotic agents. Neither patient had undergone any type of ocular surgery.

Discussion

Lattice degeneration of the retina is the most important clinically recognizable precursor of rhegmatogenous retinal detachment.[7] In one clinical series of 1,300 patients without known ocular disease, lattice lesions were found in at least one eye of 7.1% of the patients.[8] In 800 consecutive autopsy eyes, 10.6% of the patients

had lattice degeneration.[9] Lattice degeneration is most commonly found in myopic individuals[7-9,11,12] and may be hereditary.[13,14]

Retinal detachment occurs more frequently in patients with pigment dispersion syndrome and pigmentary glaucoma.[2,6] The relationship between these two entities has not been adequately explained. Additionally, the interrelationships between lattice degeneration, pigment dispersion syndrome, and myopia are incompletely understood. Patients with pigment dispersion syndrome are usually myopic. Myopia appears to facilitate the phenotypic expression of pigment dispersion syndrome, which complicates statistical evaluation of our data.

Our data suggest an increased prevalence of lesions predisposing to retinal detachment in patients with pigmentary glaucoma and pigment dispersion syndrome. However, our use of historical control subjects necessitates analysis of different populations, examination methods, and diagnostic criteria. Unfortunately, a large, nonreferred, population-matched pool of patients to use as concurrent control subjects does not exist at our institution. The large series described by Byer,[8] a nonreferred, nonselected group of patients without known ocular disease, is an adequate control group. It offers the statistical power conferred by the large number of patients examined. The diagnostic criteria for lattice degeneration were the same as ours.

Other studies of lattice degeneration are less adequate control groups. For example, Hyams and Neumann[15] found lattice lesions in only 15 of 332 myopic eyes (4.5%) examined, but included only lesions with white lines. They found what they referred to as snail-track degeneration in 36 eyes (10.8%), but did not specify any diagnostic criteria other than white dots. Some lesions designated as snail-track degeneration by other authors may represent one appearance of lattice degeneration, but other lesions manifesting similar white dots without other specific clinical signs of lattice degeneration may be of no clinical importance.[7] Additionally, Hyams and Neumann[15] did not specify how many eyes had both types of lesions. Byer's diagnostic criteria,[8] conversely, are strict and widely accepted.

Karlin and Curtin[11] found the prevalence of lattice degeneration to increase with increasing axial length, with prevalences as high as 11% to 15% of eyes with axial lengths over 30 mm. Celorio and Pruett,[12] however, noted an inverse relationship between the prevalence of lattice degeneration and axial length within the myopic population, with a peak prevalence of 40.9% for eyes with an axial length of 26 mm. Both of these studies examined populations of referred patients; the patients in the study by Karlin and Curtin[11] were referred from a myopia clinic and the patients in the study by Celorio and Pruett[12] were referred from a retinal practice. The inconsistency between the results of these two studies and Byer's series is probably explained by this selection bias.

Byer[8] found that 7.1% of 1,300 patients had lattice lesions in at least one eye. He included a graphic representation of the distribution of refractive errors in the eyes with lattice degeneration and for all of the eyes studied. By interpreting these data numerically and comparing them to ours, we found the prevalence of lattice degeneration in our patients to be significantly higher than that found in the eyes in Byer's study for every myopic refractive interval (Table).

Our cohort had a greater percentage of men (68.3%) than did the control group (41.8%). However, no correlation between gender and lattice degeneration was found in the control group.[8] No information is available about the racial composition of the control group, but a previous study[16] found no racial predilection for lattice degeneration.

Miotic therapy is also a confounding variable when trying to explain the greater risk of retinal detachment in patients with pigment dispersion. Miotic agents have been incriminated in precipitating retinal detachments.[17-19] Scheie and Cameron,[2] however, found no significant difference in the incidence of retinal detachment between patients treated with miotic agents and those who had never received them.

Pigment dispersion syndrome is uncommon in blacks[1] and blacks are generally less commonly affected by retinal detachment than are whites.[15] Comparable prevalences of lattice degeneration in blacks and nonblacks have been demonstrated in an autopsy study.[16] Thus, although race and the use of miotic agents may represent additional risk factors for retinal detachment in patients with pigment dispersion, they do not explain the high prevalence of lattice degeneration that we found.

The relationship between lattice degeneration and pigment dispersion syndrome requires further elucidation. The formation of lattice lesions may be preceded by and caused by

TABLE
PREVALENCE OF LATTICE DEGENERATION IN STUDY AND CONTROL EYES

REFRACTIVE ERROR (DIOPTERS)	STUDY EYES NO. EXAMINED	STUDY EYES NO. WITH LATTICE DEGENERATION (%)	CONTROL EYES* NO. EXAMINED	CONTROL EYES* NO. WITH LATTICE DEGENERATION (%)	P VALUE†
−6.12 or more	34	6 (17.6)	51	4 (7.8)	.17
−3.12 to −6.00	30	5 (16.7)	241	22 (9.1)	.19
−0.12 to −3.00	41	8 (19.5)	1,193	65 (5.4)	.001
Emmetropia and hyperopia	14	0	1,126	32 (2.8)	.52
Total myopia	105	19 (18.1)	1,485	91 (6.1)	.001

*Adapted from Byer's data.[8]
†Mantel-Haenszel chi-square statistic.

chronic localized vitreoretinal traction.[20] The reason for the vitreoretinal traction in these patients, however, has not been explained. Pigment dispersion syndrome results from mechanical rubbing of an abnormally posteriorly positioned midperipheral iris against the anterior zonular packets.[21] Why the midperipheral iris is concave in pigment dispersion syndrome remains unknown.

Two possible explanations may account for this relationship. The first explanation is that both are inherited and that the gene loci are closely linked. The second explanation is that a single gene predisposes to both conditions. A structural abnormality of the middle third of the eye that causes the peripheral iris to be concave in configuration (causing pigment dispersion) and the vitreous base/anterior retina to be drawn anteriorly (causing peripheral retinal degeneration) is consistent with proposed mechanisms for both conditions.

Patients with pigment dispersion syndrome have an increased prevalence of lattice degeneration and rhegmatogenous retinal detachment when compared to the general population who have similar refractive errors. The percentage of patients with pigment dispersion and retinal lesions known to be precursors of rhegmatogenous retinal detachment (25%) appears to be much higher than expected. A prospective, case-controlled study is needed to confirm our findings.

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OPHTHALMIC MINIATURE

My point is that while you should of course enjoy your sailing experience, you should take the routine marine precaution of being constantly aware that a creature the size of Yonkers, New York, could be oozing and sliming along just beneath the surface, watching you with humongous eyes. Another one of Robert's books, *The Big Book of Animal Records*, states that the eye of a giant squid can get to be—this is an Amazing True Nature Fact, coming up here—16 inches across. Think about that. Think about the size of the whole *eyeball*. Think of the pranks you could play if you got hold of an eyeball like that.

Dave Barry, *Dave Barry's Greatest Hits*
New York, Ballantine Books, 1988, p. 223

Hypotonous Maculopathy After Trabeculectomy With Subconjunctival 5-Fluorouracil

Robert L. Stamper, M.D., Matthew G. McMenemy, M.D., and Marc F. Lieberman, M.D.

Long-term success in trabeculectomy has been enhanced in recent years by postoperative subconjunctival 5-fluorouracil injections and intraoperative mitomycin C applications. During 1990 and 1991, after trabeculectomy with a small scleral flap (2 × 3 mm) augmented by antimetabolite therapy, hypotonous maculopathy developed in eight eyes of six patients. The maculopathy was characterized by loss in visual acuity, retinal striae, and choroidal folds without evidence of vascular leakage. The average loss in visual acuity was four Snellen lines. Visual acuity did not return to preoperative levels even when the hypotony could be reversed. Reversing the hypotony with various strategies aimed at stimulating subconjunctival scarring has been relatively ineffective.

During that same period, an additional seven eyes in six patients had prolonged hypotony but without development of maculopathy. Features common to patients who developed maculopathy included age (mean age, 46 years; range, 32 to 60 years) and myopia (mean, −7.5 diopters; range, −0.75 to −11.75 diopters). The patients with hypotony but no maculopathy were older (mean age, 73 years; range, 63 to 82 years) and were closer to emmetropia (mean, −1.11 diopters; range, +1.50 to −9.00 diopters). The means of the ages and refractive errors were statistically significantly different in the two groups (P = .007 and .04, respectively). Trabeculectomy with adjunctive antifibrosis therapy should be used with caution in young myopic patients.

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From the Department of Ophthalmology, California Pacific Medical Center (formerly Pacific Presbyterian Medical Center), San Francisco, California. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York, New York; and by the Pacific Vision Foundation, San Francisco, California. This study was presented at the American Glaucoma Society Meeting, Dec. 13,1991, San Diego, California.

Reprint requests to Robert L. Stamper, M.D., Department of Ophthalmology, California Pacific Medical Center, 2340 Clay St., San Francisco, CA 94115.

During 1990 and 1991, we observed the development of hypotonous maculopathy in several patients after treatment of uncontrolled glaucoma with a short-flap trabeculectomy supplemented by postoperative subconjunctival 5-fluorouracil injections. This condition consisted of choroidal folds behind the macula, which significantly reduced visual acuity. This complication developed in eight eyes of six patients.

An additional group of seven eyes in six patients was identified with persistent hypotony but no maculopathy. The patients had been treated similarly with short-flap trabeculectomies and either postoperative subconjunctival 5-fluorouracil injections or intraoperative mitomycin C application. We studied hypotonous maculopathy and identified risk factors for the development of this sight-threatening complication of otherwise successful filtering operations.

Material and Methods

We reviewed the records of all eyes examined during 1990 and 1991 with postfiltration intraocular pressures of 6 mm Hg or less that lasted six or more weeks. A short-flap (rectangular scleral flap extending 2 mm posteriorly from the anterior portion of the corneoscleral limbus and 3 mm in width) trabeculectomy combined with intraoperative application of mitomycin C or postoperative subconjunctival injections of 5-fluorouracil was performed on all eyes. A corneoscleral limbus–based conjunctival flap was fashioned at least 7 to 8 mm from the corneoscleral limbus. When mitomycin C was

used, one drop of 0.5-mg/ml solution was placed on the tip of a cellulose sponge, after which the soaked piece of sponge was placed between the limbal-based conjunctival flap and the sclera for five minutes. When 5-fluorouracil was used, five to eight 0.1-ml subconjunctival injections of 50-mg/ml concentration were administered 180 degrees away from the operative site during the first two postoperative weeks. The scleral flap was closed with a single 10-0 nylon suture at each corner. The conjunctival flap was sutured by using a closely placed running suture of 10-0 nylon, 11-0 polyester, or 9-0 polyglactin swaged to a noncutting, blood-vessel needle (for example, Ethicon BV-75-3 or BV-100-3, Ethicon, Inc., Summerville, New Jersey) to provide a watertight seal. Some eyes had the same filtering procedure combined with extracapsular cataract extraction and posterior chamber intraocular lens implantation within the capsule.

Information that included age, race, type of glaucoma, and preoperative refractive error (spherical equivalent) was collected on each patient, and the results were tabulated. The group with maculopathy consisted of eight eyes from six patients. Their data were compared, using the Student's *t*-test, to a control group of seven eyes from six patients that were operated on with similar techniques in the same period. These control eyes had comparable hypotony of the same or longer duration and yet did not develop detectable maculopathy.

When two eyes from the same patient were involved, the patient was counted only once for the determination of the statistics regarding age. With the other quantitative parameters, the data were calculated using only one eye of a patient and with both eyes in the three patients in whom this occurred. Because no significant differences were found in the two methods of calculation, all affected eyes were included in the results.

Case Reports

Case 1

A 32-year-old man with pigmentary glaucoma was first seen by the Glaucoma Service at our institution in August 1990. Intraocular pressures ranged from 28 to 42 mm Hg in both eyes despite topical use of timolol maleate, epinephryl borate, pilocarpine 4%, and apraclonidine 1%. The patient's preoperative visual acuity was R.E.: 20/20 with a −7.00 sphere and L.E.: 20/20 with a −8.00 sphere.

On Sept. 19, 1990, a short-flap trabeculectomy with watertight limbal-flap conjunctival closure was performed on the right eye. Eight subconjunctival 5-mg injections of 5-fluorouracil were administered during the first two postoperative weeks. Early intraocular pressures ranged between 0 and 4 mm Hg and visual acuity fluctuated between counting fingers and 20/400.

One month postoperatively, macular and disk swelling was noted. The patient's visual acuity was 20/200 and intraocular pressure was 7 mm Hg. Fluorescein angiography showed no vascular leakage. Two months postoperatively, visual acuity had improved to 20/80 with intraocular pressure increasing to 9 mm Hg. However, macular folds, disk elevation, and disk hyperemia persisted.

On Dec. 6, 1990, because of an intraocular pressure of 47 mm Hg in the left eye, a short-flap trabeculectomy with watertight limbal-flap closure was performed in that eye. To avoid the complication of hypotony, the scleral flap was sutured tighter than usual with several sutures. Postoperatively, the patient received six 5-mg injections of 5-fluorouracil over a two-week period.

Approximately 12 days postoperatively, the intraocular pressure had increased to 16 mm Hg in the left eye. One of the nylon sutures in the scleral flap was lysed by using the argon laser and a Hoskins lens. The intraocular pressure decreased immediately to 4 mm Hg. One day after the laser suture lysis, the intraocular pressure was 2 mm Hg and visual acuity had decreased to counting fingers. Six weeks postoperatively, intraocular pressure had increased to 7 mm Hg and visual acuity could not be corrected to better than 20/100.

Because of the persistence of macular and epiretinal folds, diathermy was applied on seven separate occasions to the periphery of the left bleb and trichloroacetic acid was applied on three separate occasions. Fifteen months postoperatively in the right eye, best-corrected visual acuity was 20/40 and the intraocular pressure was 8 mm Hg. Thirteen months postoperatively in the left eye, best-corrected visual acuity was 20/100 and the intraocular pressure was 10 mm Hg. The choroidal folds in both eyes remained unchanged (Figs. 1 and 2). Three retinal specialists disagreed as to the presence or absence of a fine epiretinal membrane overlying the left macula.

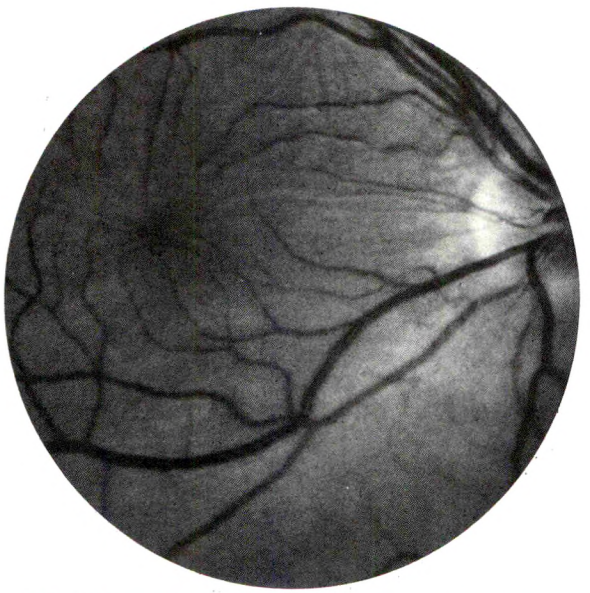


Fig. 1 (Stamper, McMenemy, and Lieberman). Case 1. Red-free photograph of the right fundus 15 months postoperatively showing macular striae.

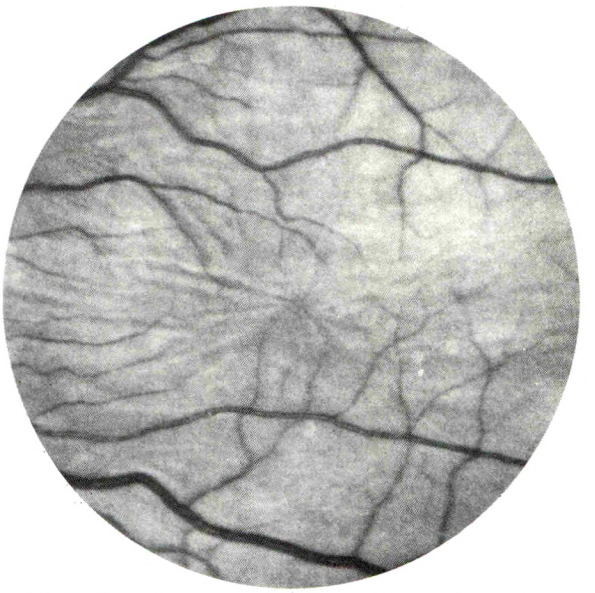


Fig. 2 (Stamper, McMenemy, and Lieberman). Case 1. Red-free fundus photograph of the left eye at 13 months postoperatively, which illustrates the macular striae associated with prolonged hypotony.

Eighteen months postoperatively in the left eye, a surgical revision of the trabeculectomy site was performed, which included resuturing the scleral and conjunctival flaps. The intraocular pressure increased to 15 mm Hg. Six months after the second surgical procedure, visual acuity in the left eye had improved to 20/50 and the choroidal folds had lessened.

Case 2

A 53-year-old woman had diabetes of five years' duration that was controlled with oral tolazamide, 100 mg per day. Additional medical problems included hypertension of 25 years' duration and asymmetric primary open-angle glaucoma of 12 years' duration. She had undergone focal argon laser treatment to the left fundus for diabetic retinopathy in 1988. In May 1990, intraocular pressure in the left eye was 21 and was 25 mm Hg during treatment with timolol maleate 0.5%, twice a day; dipivefrin 0.1%, twice a day; and pilocarpine, 2% four times a day. At initial examination, the visual acuity in the left eye was 20/15 with a refraction of -4.25 $+0.50 \times 31$. The patient had undergone previous argon laser trabeculoplasty for 360 degrees of her left eye and was intolerant of oral carbonic-anhydrase–inhibitor medications.

On May 16, 1990, a short-flap trabeculectomy with watertight conjunctival closure was performed on the left eye. During the first two postoperative weeks, seven 5-mg injections of 5-fluorouracil were administered subconjunctivally. On the first postoperative day, the anterior chamber was shallow centrally and peripherally; by nine days postoperatively, the anterior chamber had deepened with an improvement in visual acuity to 20/80. Two weeks postoperatively, visual acuity had improved to 20/40. However, one month postoperatively, visual acuity had decreased to 20/80, with an intraocular pressure of 6 mm Hg.

On July 13, 1990, 1½ months postoperatively, intraocular pressure was 4 mm Hg in the left eye and the disk was noted to be swollen. Two months later, visual acuity had decreased to 20/200. Seven months postoperatively, the left eye had macular striae, papilledema, and visual acuity of 20/200. The intraocular pressure was 6 mm Hg.

These clinical signs persisted through nine postoperative months. In February 1991, because of an intraocular pressure of 6 mm Hg, superficial diathermy was applied to the periphery of the bleb to induce scarring and increase the intraocular pressure. Six additional diathermy treatments were performed during the next three months. Intraocular pressure gradually increased from 7 to 10 mm Hg. However, visual acuity improved only to 20/100. Subsequently,

trichloroacetic acid was applied three times to the filtering site. Intraocular pressure stabilized at 12 mm Hg. Eighteen months postoperatively, the visual acuity had improved to 20/50. The choroidal folds remained essentially unchanged.

Case 3

A 60-year-old woman had had pseudoexfoliative glaucoma in the left eye since 1984. Argon laser trabeculoplasty had been performed on the left eye in 1985 and again in 1987. Despite levobunolol and pilocarpine inserts, her intraocular pressure was 27 mm Hg in the left eye in December 1990. The patient was intolerant to pilocarpine drops and oral carbonic-anhydrase inhibitors. Because of progression in the cup/disk ratio and visual field defects, a filtration procedure was recommended. Preoperative refraction was -1.00 $+0.50 \times 180$ in the left eye with a visual acuity of 20/20. On the day before surgery, the intraocular pressure in the left eye had increased to 47 mm Hg.

On Feb. 13, 1991, a short-flap trabeculectomy with a watertight limbal-flap conjunctival closure was performed on the left eye. Postoperatively, the patient developed a transient shallow anterior chamber. In the first two postoperative weeks, she received five 5-mg subconjunctival injections of 5-fluorouracil. A diffuse choroidal detachment developed ten days postoperatively. Visual acuity was 20/100 with an intraocular pressure of 4 mm Hg. During the next two months, the choroidal effusions gradually resolved, but visual acuity did not improve to preoperative levels.

Three months postoperatively, visual acuity was refractable to 20/70. The intraocular pressure remained at 4 mm Hg. Macular changes consistent with hypotony were noted. Four months postoperatively, superficial diathermy was applied to the bleb periphery. The intraocular pressure increased to about 8 mm Hg and the best-corrected visual acuity improved temporarily to 20/50. However, the intraocular pressure again decreased to the 3- to 4-mm Hg range and visual acuity also decreased to 20/100. Trichloroacetic acid was applied twice to the filtering bleb periphery. Ten months postoperatively, the intraocular pressure was 6 mm Hg and visual acuity had improved to 20/30. The macular changes were still faintly visible.

Case 4

A 33-year-old man had primary open-angle glaucoma that was first diagnosed in 1988. Despite argon laser trabeculoplasty and maximum medical therapy, his intraocular pressures were 30 mm Hg in the right eye and 26 mm Hg in the left eye. His preoperative visual acuity was R.E.: 20/40 with a -10.50 sphere and L.E.: 20/70 with a refraction of $-12.00 + 0.50 \times 83$. The cup/disk ratios were greater than 0.9 bilaterally, with evidence of myopic degeneration in both eyes.

On Nov. 14, 1990, a short-flap trabeculectomy with watertight closure of the limbal conjunctival flap was performed on the right eye. Postoperatively, five 5-mg subconjunctival injections of 5-fluorouracil were administered inferiorly for two weeks. Although shallowing of the anterior chamber was noted in the immediate postoperative week, the chamber reformed by two weeks. Three weeks postoperatively, visual acuity was 20/400, the intraocular pressure was 3 mm Hg, the anterior chamber was deep, no leak in the bleb was present, and no choroidal detachment or other additional abnormality was seen. Retromacular choroidal folds typical for hypotonous maculopathy were first noted. One month postoperatively, the intraocular pressure had increased to 10 mm Hg and visual acuity was 20/100. By six weeks postoperatively, the intraocular pressure was 11 mm Hg and visual acuity had stabilized at 20/70. The macular folds remained unchanged.

On Dec. 20, 1990, a short-flap trabeculectomy with watertight closure of a limbal conjunctival flap was performed on the left eye. Five 5-mg subconjunctival 5-fluorouracil injections were administered for the first two postoperative weeks. Three weeks postoperatively, visual acuity was counting fingers at 2 feet and choroidal folds could be seen in the macular area. One month postoperatively, a fluorescein angiogram of the left eye showed macular striae and choroidal folds, but no leakage of fluorescein was appreciated (Figs. 3 and 4). Between two and four months postoperatively, eight separate sessions of multiple superficial diathermy applications were performed on the perilimbal and posterior conjunctiva of the left eye to reduce the bleb size. The intraocular pressure could not be increased to more than 4 mm Hg.

During the fifth postoperative month, trichloroacetic acid was applied several times to the periphery of the bleb. Nine months postoperatively, visual acuity had improved only to 20/300, the intraocular pressure remained at 4 mm Hg, and the retromacular choroidal folds remained unchanged.

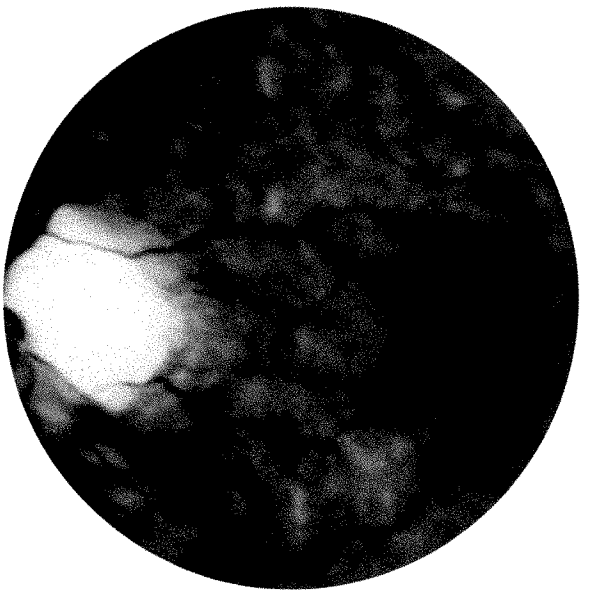


Fig. 3 (Stamper, McMenemy, and Lieberman). Case 4. Red-free fundus photograph of the operated-on eye one month postoperatively showing macular striae.

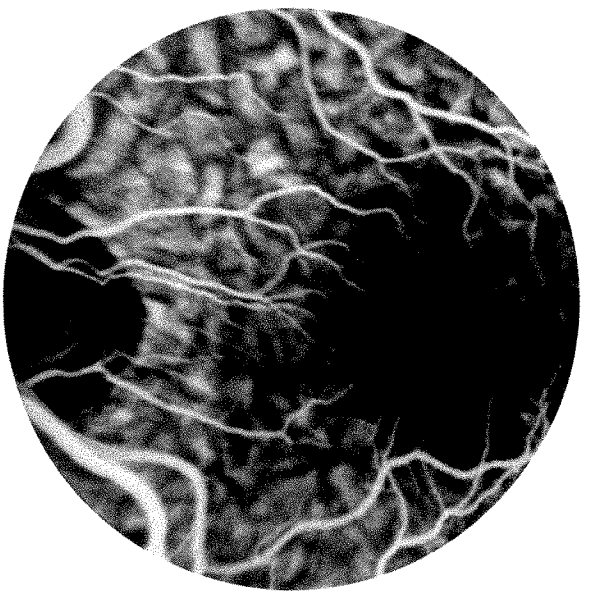


Fig. 4 (Stamper, McMenemy, and Lieberman). Case 4. Late venous phase fluorescein angiogram one month postoperatively showing choroidal folds but no leakage.

Case 5

A 38-year-old myopic man referred to the Glaucoma Service of our institution had a history of chronic uveitis associated with glaucoma in his left eye. The patient was using maximum medical therapy (a topical beta-blocker, a topical miotic agent, and an oral carbonic-anhydrase inhibitor). His visual acuity was R.E.: 20/20 and L.E.: 20/25−2 with a refraction of −4.50 +1.25 × 89 in the right eye and a refraction of −4.50 + 1.25 × 99 in the left eye. Intraocular pressures by applanation tonometry were 20 mm Hg in the right eye and 64 mm Hg in the left eye. The angles were considered to be open 360 degrees in both eyes, with heavy pigmentation in the left eye. Moderate cells and flare were present in the anterior chamber. The cells appeared to be true cells and not pigment particles. Exfoliative material was seen on the left lens surface and iris margin. The cup/disk ratio was 0.3 in the right eye and 0.8 in the left eye. The diagnosis was considered to be open-angle glaucoma associated with uveitis and pseudoexfoliation.

On March 27, 1991, a short-flap trabeculectomy with watertight closure of the limbal conjunctival flap was performed on the left eye. Postoperatively, seven 5-mg subconjunctival 5-fluorouracil injections were administered into the inferior fornix over a two-week period. Exuberant filtration was encountered with a perilimbal bleb involving more than 6 clock hours. No bleb leakage could be demonstrated. Intraocular pressures ranged between 0 and 2 mm Hg during the first four weeks. Visual acuity remained at 20/400.

Approximately one month postoperatively, choroidal effusions were first noted, which resolved after about ten days. However, choroidal folds, disk swelling, and peripapillary hemorrhage were seen 6½ weeks postoperatively. At that time in the left eye, the intraocular pressure was 4 mm Hg and visual acuity was 20/200. The low intraocular pressure, choroidal folds, and poor visual acuity persisted through the sixth postoperative month, when the patient was lost to follow-up.

Case 6

A 60-year-old man, first seen by the Glaucoma Service in July 1990, had advanced primary open-angle glaucoma that was uncontrolled with maximal topical medical therapy. His visual acuity was R.E.: 20/30+ with a refraction of −11.50 +1.00 × 145 and L.E.: 20/100− with a refraction of −11.00 +0.75 × 13. Intraocular pressures ranged from 24 to 32 mm Hg. The fundus showed normal maculae and greater than 0.9-disk-diameter cups in both eyes. Visual fields disclosed bilateral paracentral scotomata with splitting of fixation. Argon laser trabeculoplasties were unsuccessful in controlling the intraocular pressure.

A trabeculectomy was performed on the left eye in September 1990. Eight postoperative injections of 5-fluorouracil were administered over a two-week period. Postoperatively, the intraocular pressures remained in the 4- to 8-mm Hg range and visual acuity decreased to 20/400. Characteristic choroidal folds were present in the macula. During the first postoperative month, the thin superonasal bleb enlarged along the perilimbal area nasally and inferiorly toward the 5 o'clock meridian. Despite numerous attempts to reduce the bleb over the next five months, including three trichloroacetic acid applications and one application of superficial diathermy. The visual acuity never improved to better than 20/400. Ten months postoperatively, the visual acuity and macula findings were unchanged.

Because of intraocular pressures that ranged from 20 to 24 mm Hg in the right eye despite maximally tolerated medical therapy, a trabeculectomy was performed in the right eye on March 20, 1991. Only two subconjunctival injections of 5-fluorouracil (total, 12.5 mg) were administered in the postoperative period. However, a large, thin-walled bleb developed superonasally and then subsequently extended temporally around the corneoscleral limbus to the 7 o'clock meridian. Intraocular pressures remained less than 3 mm Hg for the first two postoperative weeks and then spontaneously increased to the 10- to 12-mm Hg range. Visual acuity was counting fingers at 3 feet. Choroidal folds were noted in the macula one month postoperatively.

Three months postoperatively, the intraocular pressure suddenly and inexplicably decreased to 7 mm Hg. Over the next four months, the visual acuity slowly improved to 20/50, but did not improve beyond that level. Choroidal folds persisted. Attempts to reduce the size of the large filtering bleb with trichloroacetic acid, superficial diathermy, and cryoprobe applications were not successful. Fifteen months postoperatively, the intraocular pressure in the right eye ranged from 2 to 4 mm Hg, and visual acuity was 20/60. Despite careful observation, no cyclodialysis cleft or choroidal detachment could be found.

Results

The information regarding age; race; diagnosis; affected eye; preoperative refraction, intraocular pressure, and visual acuity; postoperative intraocular pressure, best-corrected visual acuity, and change in the best-corrected visual acuity; and duration of persistent hypotony was tabulated for eyes that developed maculopathy (Table 1) and for eyes that did not develop maculopathy (Table 2). A trabeculectomy accompanied by postoperative 5-fluorouracil injections was performed on eyes that developed maculopathy associated with hypotony. Trabeculectomy with 5-fluorouracil, trabeculectomy with mitomycin C, or combined cataract extraction and trabeculectomy with either 5-fluorouracil or mitomycin C was performed on eyes with hypotony but no maculopathy. Only one eye had selective postoperative laser suture lysis performed and this eye was in the group with maculopathy. All eyes were phakic in both groups except for one eye in the group without maculopathy on which a combined trabeculectomy, cataract extraction, and lens implantation was performed. The number of 5-fluorouracil injections each eye received varied between two and eight per eye and was not significantly different between the two groups.

Analysis of the results showed a mean age of 50 years among patients with maculopathy (range, 33 to 60 years) (Table 3). The group with hypotony but without maculopathy had a mean age of 74 years (range, 63 to 82 years). Diagnoses in the maculopathy group included open-angle glaucoma, pigmentary glaucoma, uveitic glaucoma, and exfoliative glaucoma. Ethnicity was broad-based and encompassed Asian, black, white, and Hispanic patients. Similar ranges of diagnoses and ethnicity were noted in the patients without hypotony.

In the group with maculopathy, six of the eight involved eyes were left eyes. Preoperative refraction had a mean spherical equivalent of −7.50 diopters and a range of −0.75 to −11.75 diopters. The group without maculopathy had a mean preoperative spherical equivalent of −1.11 diopters with a range of +1.50 to −9.00 diopters. The group with maculopathy was younger and more myopic than the group without maculopathy; these differences were statistically different (Table 3). The groups were not statistically significant with regard to postoperative intraocular pressure or duration of hypotony. Only one eye in the group with hypotony but without maculopathy had a refractive error larger than −1.25 diopters. This eye had a considerable cataract and the axial length was 24 mm, which suggested that the cataract was responsible for most of the 9 diopters of myopia.

Preoperative intraocular pressures ranged

TABLE 1
CHARACTERISTICS OF PATIENTS WITH MACULOPATHY

PATIENT NO., AGE (YRS), RACE OR ETHNICITY	EYE AFFECTED	TYPE OF GLAUCOMA	SPHERICAL EQUIVALENT (DIOPTERS)		POSTOPERATIVE INTRAOCULAR PRESSURE (MM HG)		MONTHS* POSTOPERATIVE		PREOPERATIVE VISUAL ACUITY		VISION CHANGE† (LINES)	
			R.E.	L.E.	R.E.	L.E.	R.E.	L.E.	R.E.	L.E.	R.E.	L.E.
1, 32, white	Both eyes	Pigmentary	−8.375	−10.00	8	10	10	7	20/20	20/20	−4	−4
2, 53, black	L.E.	Primary open-angle	—	−4.00	—	10	—	12	—	20/25	—	−7
3, 33, Asian	L.E.	Primary open-angle	—	−11.75	—	4	—	6	—	20/70	—	−4
4, 60, white	L.E.	Exfoliative	—	−0.75	—	4	—	5	—	20/20	—	−8
5, 38, Hispanic	L.E.	Uveitic	—	−3.875	—	2	—	3	—	20/25	—	−7
6, 60, white	R.E.	Primary open-angle	−11.00	—	10	—	9	—	20/30	—	−3	—

*Postoperative month at which data were collected.
†Number of lines of change in Snellen visual acuity from preoperative level at postoperative month.

between 20 and 64 mm Hg in the maculopathy group and 18 to 39 in the group without maculopathy. Preoperative visual acuity varied from 20/20 to 20/100 in the maculopathy group, with postoperative visual acuities ranging from 20/50 to 20/300. On average, visual acuity as graded by Snellen charts decreased by four lines per eye. In all cases, best-corrected postoperative visual acuity was less than best-corrected preoperative visual acuity. The best postoperative visual acuity obtained in this group of patients was 20/30. None of the patients developed a considerable cataract.

In contrast, the preoperative visual acuity in the eyes with hypotony but without maculopathy ranged from 20/20 to 20/70, while postoperative visual acuities ranged from 20/20 to 20/80. Visual acuity as graded by Snellen charts decreased on average less than one line per eye. The maximum loss of visual acuity in this group (by definition) was two lines of Snellen acuity.

TABLE 2
CHARACTERISTICS OF PATIENTS WITHOUT MACULOPATHY

PATIENT NO., AGE (YRS), RACE OR ETHNICITY	EYE AFFECTED	TYPE OF GLAUCOMA	SPHERICAL EQUIVALENT (DIOPTERS)		POSTOPERATIVE INTRAOCULAR PRESSURE (MM HG)		MONTHS* POSTOPERATIVE		PREOPERATIVE VISUAL ACUITY		VISION CHANGE† (LINES)	
			R.E.	L.E.	R.E.	L.E.	R.E.	L.E.	R.E.	L.E.	R.E.	L.E.
7, 74, white	L.E.	Primary open-angle	—	+0.50	—	5	—	7	—	20/60	—	+1
8, 69, Hispanic	R.E.	Primary open-angle	−9.00	—	4	—	18	—	20/50	—	0	—
9, 74, white	L.E.	Primary open-angle	—	+1.50	—	4	—	8	—	20/70	—	+3
10, 63, white	R.E.	Primary open-angle	+0.50	—	4	—	5	—	20/25	—	−0.5	—
11, 77, white	R.E.	Primary open-angle	−1.25	—	—	6	—	6	—	20/40	—	+1
12, 82, white	Both eyes	Primary open-angle	Plano	Plano	1	3	7	32	20/25	20/20	−2	−1

*Postoperative month at which data were collected.
†Number of lines of change in Snellen visual acuity from preoperative level at postoperative month.

Discussion

The findings of this study suggest that a specific maculopathy, characterized by retinal and choroidal folds, may be associated with prolonged hypotony after trabeculectomy combined with antimetabolite therapy in eyes of patients who are young and myopic. This maculopathy may be associated with considerable and permanent visual loss. While comparable prolonged hypotony developed in eyes from older patients who were not myopic, no instance of maculopathy was seen in this group.

Complications associated with glaucoma filtering operations include endophthalmitis, bleb leakage and scarring, choroidal detachment, cataract, and hypotony.[1-3] Persistent hypotony, secondary to any cause, has several clinical features, including thickening of the cornea with striae at Descemet's membrane, shallow anterior chamber, peripheral anterior synechiae, suprachoroidal hemorrhage, choroidal detachment, disk swelling, tortuous retinal vessels, thickening as well as striae of the retina, and cataract.[2-7] Although some of these features appeared in both of our groups with hypotony, none but the retinal striae could be associated with prolonged loss in visual acuity.

The goal of glaucoma filtering operations is to reduce the intraocular pressures to a level that will prevent further optic nerve damage. Compared to the full-thickness filtering operations such as trephination, thermal sclerostomy, and posterior lip sclerectomy, trabeculectomy results in less hypotony and cataract formation.[1,8,9] However, the costs of trabeculectomy are a higher intraocular pressure and shortened postoperative effectiveness of the procedure. Because of its reduced rate of hypotony compared to the full-thickness procedures, trabeculectomy has become the most commonly used incisional surgical procedure for the treatment of glaucoma. Recently, modifications to the basic trabeculectomy technique have been proposed to improve the effectiveness of trabeculectomy without sacrificing its relative safety. These modifications have included the short-flap technique (which theoretically allows easy postoperative laser suture lysis), laser suture lysis, postoperative 5-fluorouracil injection, and intraoperative mitomycin C application.[10-14]

Paradoxically, the glaucomatous eyes of young patients that seem to be at risk for hypotonous maculopathy are also more likely to show failure of filtration after trabeculectomy unless additional steps are taken to slow the postoperative scarring process.[8] Furthermore, because these patients have a long expected life span, we wish to keep the intraocular pressure low enough to prevent further optic nerve damage for a longer period of time than in the eyes of their older counterparts. Short-flap trabeculectomy, laser suture lysis, antimetabolite therapy, intraoperative mitomycin C application, and postoperative 5-fluorouracil injections have been suggested as effective means to achieve a lower intraocular pressure for longer postoperative periods in eyes at increased risk for failure of filtration. Conversely, better reduction of intraocular pressure may result in considerable and permanent loss of vision. Surgeons thus face a serious dilemma.

No evidence exists to implicate the size of the trabeculectomy flap as influencing either the incidence or degree of hypotony. Hypotony occurs with long trabeculectomy flaps as well as with short flaps.[1,2,15] However, an increased rate of hypotony has been associated with the use of antifibrosis therapy (unpublished data, Lytle, R. A., Reed, J. E., Pruett, R. C., and Simmons, R. J., "Hypotony maculopathy following glaucoma filtering surgery," presented at the American Academy of Ophthalmology meeting, November 1990). Furthermore, the results of our own series suggest that antifibrosis therapy may contribute to difficulty in inducing scarring of a filtering bleb after application of superficial diathermy, trichloroacetic acid, or cryotherapy. Ten to 20 conjunctival applications of cryotherapy for two to three seconds have been recommended as effective in this kind of situation (unpublished data, Ball, S. F., Discussion of Lytle and associates, "Hypotony maculopathy following glaucoma filtering surgery," presented at the American Academy of Ophthalmology meeting, November 1990). These recommendations have not been generally accepted. In any case, surgical revision of the filtering site including additional suturing of the trabeculectomy flap may be indicated in eyes with persistent hypotony.[6] The best time to intervene remains to be demonstrated, but our experience suggests that, in a young myopic patient with an eye with postoperative hypotony that fails to return to the preoperative visual acuity level within 12 weeks, some attempt at reducing filtration should be considered.

The incidence of hypotonous maculopathy is uncertain but is probably not rare. Appiah and Hirose[16] found that trabeculectomy was rarely

TABLE 3
MEANS (± STANDARD DEVIATION) OF PATIENTS WITH MACULOPATHY AND THOSE WITHOUT MACULOPATHY

	AGE (YRS)	SPHERICAL EQUIVALENT	POSTOPERATIVE INTRAOCULAR PRESSURE (MM HG)	MONTHS OF HYPOTONY	LINES OF VISION CHANGE*
Group with hypotony	46 (±13.2)	−6.61 (±4.44)	5.5 (±2.95)	7.33 (±3.33)	−4.33 (±2.13)
Group without hypotony	74.4 (±6.6)	−1.11 (±3.58)	3.9 (±1.6)	11.4 (±10.2)	+0.36 (±1.4)
P value	.0007†	.04†	.2	.3	.0006†

*Change in Snellen lines from preoperative to postoperative at time of measurement.
†Statistically significant.

followed by premacular wrinkling compared to cataract and retinal surgical procedures. According to Lytle and associates (unpublished data, Lytle, R. A., Reed, J. E., Pruett, R. C., and Simmons, R. J., "Hypotony maculopathy following glaucoma filtering surgery," presented at the American Academy of Ophthalmology meeting, November 1990), and Stewart Ball, M.D. (unpublished data, Ball, S. F., Discussion of Lytle and associates, "Hypotony maculopathy following glaucoma filtering surgery," presented at the American Academy of Ophthalmology meeting, November 1990), such cases occur in 3% to 5% of all primary filtering operations. It is not clear why eyes of young, myopic patients seem to be at highest risk for the development of this complication. One possible explanation might relate to the reduced scleral rigidity of these eyes. Unfortunately, axial lengths were obtained for only one of the eyes in our series. Future studies might focus on this factor to see if an axial length of more than a certain value might bear some prognostic relevance.

The histopathologic characteristics of uveal and retinal edema in acute and persistent hypotony were described by Volcker and Naumann[17] in 1979. In cases of acute hypotony, the posterior choroid becomes diffusely thickened. This in turn may be followed by a peripheral choroidal detachment. The increasing choroidal volume leads to folds of Bruch's membrane as well as the retina. Cystoid degeneration, especially in the outer plexiform and inner nuclear layers, results in clumping of receptor cells on the inner sides of the folds as well as distinctive wrinkling of the inner limiting membrane.

Hypotony that lasts for months can also result in optic nerve edema, diffuse thickening of the choroid, and cystoid degeneration, especially in the macular region. Finally, hypotony that lasts many years may result in fixed hypotonous folds, loss of photoreceptors and cells of the outer retinal layers, choroidal thickening, and dilated vessels. The retinal folds become fixed by proliferation on the surface of the internal limiting membrane. Conversely, Detry-Morel, Kittel, and Lemagne[18] described a patient who developed a macular surface-wrinkling retinopathy within just a few days after trabeculectomy. Whatever the time course of surface retinal changes, such changes might explain the failure of the postoperative visual acuities to return to their preoperative levels in our patients whose hypotony was successfully reversed. The roles of choroidal folding and surface retinal change in hypotonous maculopathy and the relationship between them remain to be determined.

Apple and Rabb[19] described the pathophysiologic characteristics of optic nerve head edema and hypotony. Reduction of the tissue pressure in the prelaminar area, or increase of the pressure in the retrolaminar area of the optic nerve disrupts axoplasmic flow gradients and in turn results in disk swelling. Some of our patients did develop disk swelling without vascular leakage on fluorescein angiography.

Migdal and Hitchings[15] studied the morbidity after prolonged postoperative hypotony after trabeculectomy. They found that all patients whose visual acuity decreased by more than two lines had moderate to severe preoperative loss in visual acuity as well as cup/disk ratios greater than or equal to 0.8. Most, but not all, of our patients met these criteria. Migdal and Hitchings[15] also found that the patients who

had a longer period of postoperative hypotony as well as those who had choroidal effusions ultimately had higher final intraocular pressures. This observation was not supported by our series.

Analysis of our results suggests that trabeculectomy augmented with 5-fluorouracil should be used with caution in young myopic patients. Whether the short scleral flap had a role is unclear. The visual morbidity associated with prolonged hypotony, as seen in the patients mentioned previously, is not inconsequential. Paradoxically, these young patients are thought to be at high risk for filtration failure without 5-fluorouracil or mitomycin C. Thus, glaucoma specialists may face a serious dilemma with young myopic patients in need of filtration procedures.

Furthermore, the management of postoperative hypotony remains a question. Overfiltration in these same patients, perhaps fostered by the antifibrosis treatment, responded poorly to therapeutic attempts including diathermy, cryotherapy, and trichloroacetic acid application. This difficulty in inducing scarring of a large bleb at its periphery probably reflects long-lasting effects of antimetabolite treatment. Perhaps early resuturing of the scleral flap may be necessary to prevent or reduce the maculopathy.

On the basis of these observations, the treatment of young myopic patients with glaucoma who need surgery may need modification. It may require abandonment of the short-flap technique, less vigorous use of 5-fluorouracil, tight suturing of the flap with subsequent laser suture lysis, or some combination of these techniques. Further study is necessary to identify the best approach in these patients at high risk for both filtration failure without antifibrosis therapy and hypotonous maculopathy with such therapy. Study is also needed to clarify further those characteristics leading to a higher risk of hypotonous maculopathy such as scleral rigidity and axial length.

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Changes in Optic Disk Characteristics and the Number of Nerve Fibers in Experimental Glaucoma

Rohit Varma, M.D., Harry A. Quigley, M.D., and Mary Ellen Pease

We compared the change in cup/disk ratio and neuroretinal rim area-to-disk area to estimated change in the number of optic nerve fibers in 12 cynomolgus monkeys with unilateral experimental glaucoma. Changes in the cup/disk ratios and neuroretinal rim area-to-disk area were estimated from stereoscopic optic disk photographs that were obtained before and after the development of increased intraocular pressure. Change in the number of optic nerve fibers in the glaucomatous nerves was estimated by comparing them to their fellow normal nerves. A significant linear correlation was present between change in the cup/disk ratios and neuroretinal rim area-to-disk area, and estimated change in the number of optic nerve fibers ($r \geq .85$; $P < .0002$). In optic disks with initial cup/disk ratios of 0.2 to 0.3 and neuroretinal rim area-to-disk area of 0.9, an increase in the cup/disk ratio of 0.1 and a decrease of 0.1 in the neuroretinal rim area-to-disk area is associated with a 10% and 9% loss of optic nerve fibers, respectively.

In glaucoma there is preferential loss of retinal ganglion cells and their axons. This has been demonstrated in histologic studies of human eyes with chronic glaucoma and monkey eyes with chronic experimental glaucoma.[1-5] Clinicians use descriptions of the optic disk and nerve fiber layer to estimate the degree of glaucomatous optic nerve damage. Among these, the cup/disk ratio, the neuroretinal rim area, nerve fiber layer defects, and the relative nerve fiber layer height have been correlated with visual field loss.[6-11] While changes in optic disk characteristics in glaucoma generally correlate with psychophysical test results, the detailed relationship between optic disk characteristics and optic nerve fiber counts has not been well established.

We induced experimental glaucomatous damage in one eye of each of 12 monkeys and compared clinical assessments of changes in the optic disks to changes in the estimated number of nerve fibers in each optic nerve. Specifically, we investigated the relationship between changes in cup/disk ratios, neuroretinal rim area-to-disk area ratios, and changes in optic nerve fiber number.

Material and Methods

These experiments heeded the Association for Research in Vision and Ophthalmology Resolution on the Use of Animals in Research. The procedures were specifically approved by the Animal Care Committee of the Johns Hopkins University School of Medicine. Stereoscopic color optic disk photographs were obtained from both eyes of 12 cynomolgus monkeys (*Macaca fascicularis*) by using a fundus camera. Chronic increase in intraocular pressure was then induced in one eye of each monkey by treating the trabecular meshwork with argon laser with the monkey under ketamine hydrochloride sedation and intravenous sodium pentobarbital anesthesia.[12] The mean intraocular pressure in the laser-treated eyes ranged from 25 to 40 mm Hg and the durations of intraocular pressure increase ranged from four to 17

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Reprint requests to Rohit Varma, M.D., Wilmer B-23, Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21287.

months. The intraocular pressure was measured with each monkey under ketamine sedation and topical proparacaine anesthesia by using an applanation tonometer mounted on a slit lamp. Monkeys were killed after varying degrees of optic nerve damage had occurred. Just before each monkey was killed, a final set of stereoscopic optic disk photographs was obtained.

Optic nerves were fixed by sequential perfusion of paraformaldehyde and glutaraldehyde at lower concentration (1%, 1.5%, respectively) and then at higher concentration (4%, 5%, respectively). The optic nerve was marked with one razor slice at the 12 o'clock meridian before removal of a nerve cross section 2 mm posterior to the globe. The tissue was postfixed in osmium and embedded in epoxy resin. Sections 1 μm thick were stained with paraphenylenediamine. The number of optic nerve fibers was estimated with the Zeiss IBAS image analysis system (Carl Zeiss, Thornwood, New York), by a previously described technique that counts at least a 5% sample of all nerve fibers.[13] The variability in estimating nerve fiber counts with this technique is approximately 5%.[13]

Optic disk photographs were presented in random order to one observer without any information regarding the clinical data and date of photography. An eyepiece micrometer was used to measure the vertical and horizontal cup and disk diameters from the stereoscopic photographs. No correction for magnification was used as changes were studied in unitless measurements (cup/disk ratio and neuroretinal rim area-to-disk area). If we had studied absolute measurements such as rim area or cup volume, then such magnification correction would be essential. The optic disk margin was defined as the inner margin of the scleral ring and the cup margin was defined as the point of maximum inflection of the cup slope. The vertical and horizontal cup/disk ratios and the neuroretinal rim area-to-disk areas were calculated from the cup and disk diameters by assuming that the cup and the disk were elliptic. The intraobserver variation was determined by measuring each photograph once on two different days. The data were then analyzed using paired *t*-tests and regression analysis.

Results

Before the development of glaucoma, the mean vertical and horizontal cup/disk ratios for the 12 eyes were 0.29 and 0.25, respectively, and the mean neuroretinal rim area-to-disk area was 0.91. The mean increase in the vertical and horizontal cup/disk ratios with the development of glaucoma was 0.32 and 0.34, respectively, and the mean decrease in neuroretinal rim area-to-disk area was 0.36. The mean vertical and horizontal disk diameters in the 12 eyes, before the development of glaucoma, were 51 and 37 eyepiece units, respectively. The mean decrease in the vertical and horizontal disk diameters after the development of glaucoma was 1.33 and 0.25 eyepiece units, which was not statistically significant ($P = .27$, .69, respectively). The disk diameters were not corrected for changes in magnification that may be caused by increased axial length of the eye that is related to the development of glaucoma. However, if the disks had increased in size, then the disk diameters should have increased with increase in axial length of the eye because the magnification factor decreases by approximately 5% for every 1-mm increase in axial length in monkey eyes.[14] Therefore, we believe that there was no significant increase in the size of the optic disk with the development of glaucoma.

Before the induction of increased intraocular pressure, the right and left optic disks of each of the 12 monkeys were similar (Table). For example, there was no statistically significant difference between the vertical and horizontal cup/disk ratios or the neuroretinal rim area-to-disk area of fellow eyes at baseline (Table). We assumed that nerve fiber counts in fellow eyes were similar before the development of glaucoma and estimated the loss of nerve fibers by

TABLE
DIFFERENCES BETWEEN FELLOW RIGHT AND LEFT EYES OF 12 MONKEYS AT BASELINE

VARIABLE	RIGHT EYES (± STANDARD DEVIATION)	LEFT EYES (± STANDARD DEVIATION)	DIFFERENCE	P VALUE*
Vertical cup/disk ratio	0.29 (± 0.12)	0.27 (± 0.08)	0.02	.47
Horizontal cup/disk ratio	0.25 (± 0.11)	0.25 (± 0.08)	0.00	.94
Neuroretinal rim area-to-disk area	0.91 (± 0.07)	0.92 (± 0.04)	0.01	.49

*Paired *t*-test.

comparing each glaucomatous nerve to its fellow normal nerve. The percent loss of nerve fibers in the glaucomatous eyes was then correlated with the change in optic disk characteristics as determined by evaluation of photographs. The change in vertical and horizontal cup/disk ratios and change in neuroretinal rim area-to-disk areas were highly correlated with the estimated percentage loss of nerve fibers (r = .87, .85, .88, respectively) ($P < .0002$) (Figs. 1 through 3). Also, the vertical and horizontal cup/disk ratios and neuroretinal rim area-to-disk areas in the 12 glaucomatous eyes after the development of glaucoma correlated moderately well with the estimated number of optic nerve fibers that remained (r = .77, .71, .79, respectively).

There was no statistically significant difference between the two estimations by the single observer of the vertical and horizontal cup/disk ratios and neuroretinal rim area-to-disk area ratios (P = .47, .84, .49, respectively). The mean intraobserver differences between the two estimations of the vertical and horizontal cup/disk ratios and neuroretinal rim area-to-disk areas were 0.09, 0.10, and 0.04, respectively. The mean coefficients of variation for vertical and horizontal cup/disk ratio and neuroretinal rim area-to-disk area were 25%, 26%, and 3.8%, respectively. Poor stereoscopic photograghs of four of the 12 eyes appeared to be responsible for much of the variability.

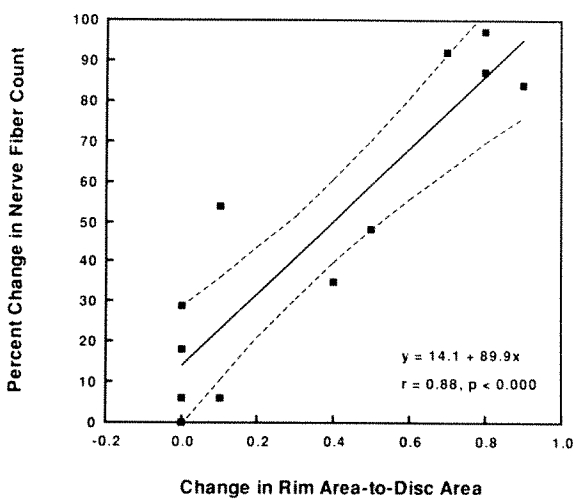


Fig. 1 (Varma, Quigley, and Pease). Scattergram and linear regression plot showing the relationship between change in neuroretinal rim area-to-disk area and estimated percent change in nerve fiber count. The 95% confidence interval of the estimates lies between the two dashed lines.

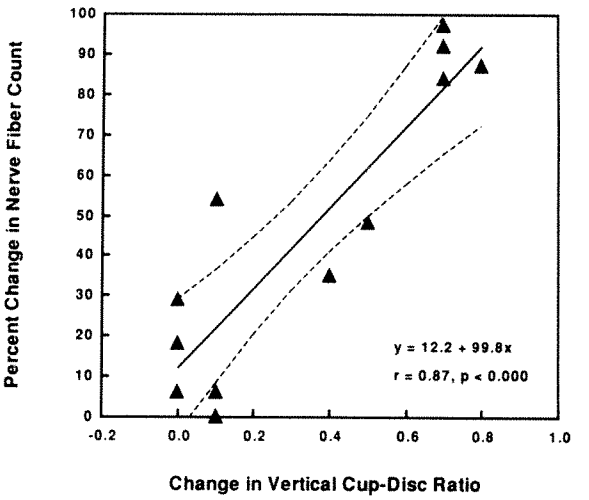


Fig. 2 (Varma, Quigley, and Pease). Scattergram and linear regression plot showing the relationship between change in vertical cup/disk ratio and estimated percent change in nerve fiber count. The 95% confidence interval of the estimates lies between the two dashed lines.

Discussion

We showed that in experimental glaucoma in monkeys, change in the vertical and horizontal cup/disk ratio and in the neuroretinal rim area-to-disk area linearly correlates with change in the number of optic nerve fibers. Thus, in optic disks with initial neuroretinal rim area-to-disk areas of 0.9, each 0.1 decrease in the neuroretinal rim area-to-disk area correlates with a loss of approximately 9% (±2.9%, 95% confidence interval) of optic nerve fibers (108,000 nerve fibers) (Fig. 1). Similarly, in optic disks with initial cup/disk ratios of 0.2 to 0.3, each 0.1 increase in the vertical or horizontal cup/disk ratio correlates with a loss of approximately 10% (±4%, 95% confidence interval) of optic nerve fibers (120,000 nerve fibers) (Figs. 2 and 3). These estimates would be different if the initial cup/disk ratios were either smaller or larger.

The appearance of the optic disk should serve as a good surrogate for optic nerve fiber counts because the optic disk is mainly composed of optic nerve fibers.[15] Additionally, optic disk assessment with the use of objective characteristics has a high intraobserver reproducibility.[16] However, baseline photographs are needed to evaluate change in the optic disk. Another drawback is the possibility that the appearance of the optic disk may change simply because of

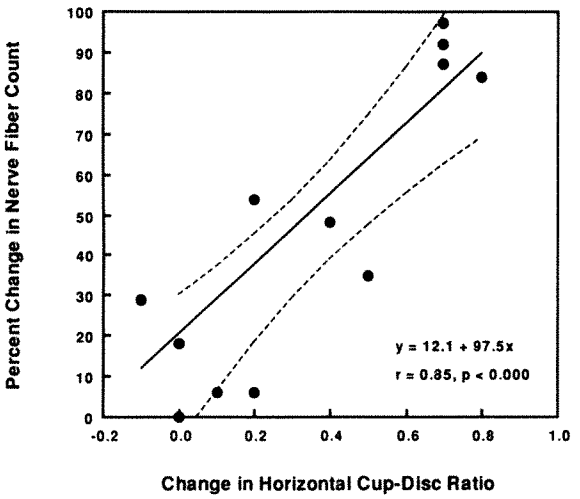


Fig. 3 (Varma, Quigley, and Pease). Scattergram and linear regression plot showing the relationship between change in horizontal cup/disk ratio and estimated percent change in nerve fiber count. The 95% confidence interval of the estimates lies between the two dashed lines.

the mechanical effects of intraocular pressure on the optic disk, which bows back the disk surface. Such a physical shift in position would not necessarily indicate the loss of nerve fibers, though it would give rise to different estimates of the cup/disk ratio and neuroretinal rim area-to-disk area. Additionally, change in the clinical appearance of the optic disk may not be as sensitive as nerve fiber layer assessment in detecting early glaucomatous optic nerve damage.[17] It may be that assessing the topographic characteristics of the optic disk or the relative peripapillary retinal nerve fiber layer height by using image analyzers may improve the evaluation of change in the optic nerve.[10] Finally, the proportion of neural tissue to glial tissue in the optic disk may vary from individual to individual. Minckler, McLean, and Tso[15] showed that the area of axonal tissue in the optic disk of monkeys varies from 94% anteriorly to 78% at the level of the sclera. Perhaps optic nerves of different individuals may have different proportions of neural and glial tissue in the optic disk. This would alter to some extent the relationship between alterations in disk appearance and loss of nerve fibers. Even though optic disk evaluation has the previously mentioned disadvantages, it still remains an objective and reproducible clinical method to assess the status of the optic nerve head in patients with glaucoma.

Although optic disk examinations can estimate the state of the optic nerve, this relationship has been largely assumed by comparing optic disk and nerve fiber layer characteristics to visual loss.[5-11] Optic disk characteristics have been associated directly with ganglion cell and optic nerve fiber loss in a few glaucomatous human and monkey eyes.[18-20] Quigley, Addicks, and Green,[18] Quigley,[19] and Johnson and associates[20] compared the cup/disk ratio and the number of nerve fibers in human and monkey eyes with glaucoma. Their data disclosed that glaucomatous eyes with larger cup/disk ratios and an atrophic nerve fiber layer have fewer optic nerve fibers. However, because these data did not contain baseline estimates of the cup/disk ratio, it is not possible to assess change in the cup/disk ratio and its effect on the number of nerve fibers. Also, the cup/disk ratios in the human studies were taken from the premortem ophthalmic records and were not read by a standardized method. Additionally, the preservation of human tissue for histologic study was variable and did not allow for ideal conditions for estimating the number of nerve fibers. We compared the change in optic disk characteristics to loss of nerve fibers under ideal conditions of tissue preservation and showed a linear correlation between them.

However, this linear relationship between change in optic disk characteristics and estimated change in the number of nerve fibers should be cautiously interpreted. Although a linear correlation fits our data, we had few cases of optic nerves with moderate damage (Figs. 1 through 3). Furthermore, if the relationship between change in neuroretinal rim area-to-disk area and change in the number of optic nerve fibers is linear, then the relationship of change in the cup/disk ratio to nerve fiber number should not be linear. For example, assume for the purpose of illustration that the normal optic disk is spheric and has a neuroretinal rim area-to-disk area of 0.9. Consider 15 such disks that develop glaucomatous damage with a decrease in their neuroretinal rim area-to-disk area ranging from 0.0 to 0.7 in increments of 0.05 (Fig. 4). The calculated changes in their cup/disk ratios would range from 0.0 to 0.57 (Fig. 4). Note that the curve describing the cup/disk ratio crosses the straight line for the neuroretinal rim area-to-disk area when both are plotted against nerve fiber loss. This occurs because the neuroretinal rim area is derived from the square of the cup diameter, whereas the cup/disk ratio is related simply to the cup diameter. Thus, if there is a linear relationship of fiber loss to change in neuroretinal rim area-

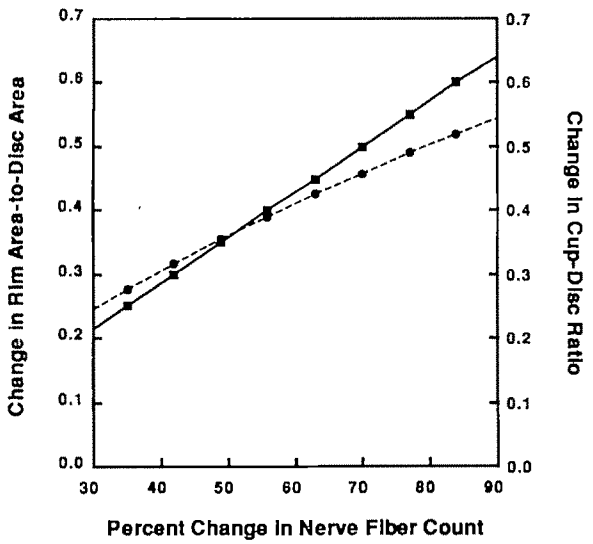


Fig. 4 (Varma, Quigley, and Pease). Model comparing change in neuroretinal rim area-to-disk area (solid line) and cup/disk ratio (dashed line) to percent change in nerve fiber count. In this model, the relationship between neuroretinal rim area-to-disk area and change in nerve fiber count is linear when compared to the nonlinear (quadratic) relationship between cup/disk ratio and change in nerve fiber count.

to-disk area, the expected relationship of fiber loss to change in cup/disk ratio would not be linear.

Yet in our data a linear function fits both relationships better than a nonlinear (quadratic) function. This may be caused by several factors. First, the difference between a quadratic and linear relationship for optic disks with initial mean cup/disk ratios of 0.3 is small and the precision of measurement of cup/disk ratios may not be as good as would be needed to demonstrate the difference between a linear or quadratic relationship (Fig. 4). Because of less than optimal stereoscopic photographs in some cases, the reproducibility of cup/disk ratio estimates was also not ideal. Second, it may be that the true relationship between both change in cup/disk ratios and neuroretinal rim area-to-disk area and change in nerve fiber count is linear but each has a different slope (as we have found). However, our explanation of having a linear relationship for neuroretinal rim area-to-disk area and a nonlinear relation for cup/disk ratio may be too simplistic to characterize the complex structure of the optic nerve head, which can vary from a three-dimensional truncated cone to a cylinder. Additionally, the proportion of neural to glial tissue probably changes with progressive optic nerve damage, leading to loss of different numbers of nerve fibers for the same unit change in cup/disk ratio or neuroretinal rim area-to-disk area. Thus, there are many factors that complicate the analysis of the relation between changes in the cup/disk ratio or neuroretinal rim area-to-disk area and nerve fiber loss.

Our study had three strengths. First, we used standard methods to estimate the neuroretinal rim area-to-disk area and the cup/disk ratios. Second, we had both baseline and final estimates of the optic disk characteristics, which allowed for the calculation of change. Third, optic nerve tissue preservation was ideal and allowed the best conditions for estimating the number of nerve fibers.

However, we studied a relatively small number of eyes. If we had more eyes with moderate damage, the relationship between optic disk characteristics and nerve fibers could have been better delineated. Another potential weakness is that we estimated the loss of nerve fibers in the glaucomatous nerve by comparing it to the contralateral normal eye. Yet, the number of nerve fibers in right and left eyes is known to vary somewhat. In histologic counts of 16 right/left pairs of normal human eyes, the 95% confidence interval for the difference between right and left eyes is 28% of the mean number of nerve fibers.[21] In a related study, we determined by automated image analysis of the optic disk that the 95% confidence interval for the difference between the neuroretinal rim area of eight right/left pairs of normal monkey eyes was similarly 25% of the mean neuroretinal rim area.[22] This variability may explain the wide range in optic nerve fiber counts among eyes with similar changes in the cup/disk ratio and neuroretinal rim area-to-disk area in our data (Figs. 1 through 3).

One potential improvement in methodology might be to use automated image analysis of disk images or to use retinal nerve fiber layer photographs before and after the development of glaucoma. Unfortunately, we did not obtain nerve fiber layer photographs or automated image analysis of the eyes in this study. These might provide more sensitive surrogates for early nerve fiber loss. Quigley and associates[17] showed that retinal nerve fiber layer defects may be more sensitive than cup/disk ratios in detecting progressive optic nerve damage in human hypertensive eyes. Image analysis is another method that would permit the calculation of various topographic characteristics of the optic nerve, including rim area and peripapillary retinal height.[10] This method has high

reproducibility[23,24] and can calculate a variety of characteristics, thereby possibly outperforming clinical assessment of the optic disk.[25]

Our data showed a direct relationship between change in optic disk characteristics and loss of optic nerve fibers in experimental glaucoma. This study thus provides some histologic support for the use of these measurements in the assessment of progressive optic nerve damage in glaucoma.

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The Influence of Exposure Duration in Transscleral Nd:YAG Laser Cyclophotocoagulation

Bruce E. Prum, Jr., M.D., Steven R. Shields, M.D., Ruthanne B. Simmons, M.D., David A. Echelman, M.D., and M. Bruce Shields, M.D.

Transscleral cyclophotocoagulation was performed in human autopsy eyes by using three Nd:YAG lasers with different durations of exposure: a pulsed, contact laser with a duration of 0.75 millisecond and a range of one to ten pulses per burst (GLase 106, Sunrise Technologies, Fremont, California); a pulsed, noncontact laser with a duration of 20 milliseconds (Microruptor 2, Lasag Medical Lasers, Thun, Switzerland); and a continuous-wave, contact laser with durations of 700 and 2,000 milliseconds (Microruptor 3, Lasag Medical Lasers, Thun, Switzerland). Tissue responses were observed with a high-magnification videographic recording technique to analyze the immediate, real-time laser effects, and by light microscopy to characterize the laser-induced lesions further. Videographically, both pulsed lasers were noted to cause mild whitening of the pigment epithelium with frequent vaporization and explosive tissue disintegration. Histologically, the 0.75-millisecond pulse typically produced the most marked epithelial disruption, referred to as an explosive-like lesion, whereas the 20-millisecond pulse more often caused moderate tissue disruption with elevation of the epithelial layers in a blister-like lesion. In contrast, the continuous-wave laser was observed videographically to produce prominent tissue whitening and puckering, seen histologically as convolution of the epithelium and coagulation of stroma, which was called a shrinkage-like lesion. Our study suggests that exposure duration influences in vitro tissue response to transscleral Nd:YAG cyclophotocoagulation, although in vivo studies and clinical trials are needed to determine which tissue response is optimum for clinical use.

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From the Department Of Ophthalmology, Duke University Eye Center, Durham, North Carolina. This study was supported by an unrestricted grant from the Barkhouser Glaucoma Research Laboratory, Duke University Eye Center.

Reprint requests to M. Bruce Shields, M.D., Duke University Eye Center, P.O. Box 3802, Durham, NC 27710.

EARLY CLINICAL EXPERIENCE with transscleral Nd:YAG laser cyclophotocoagulation has disclosed marked advantages over cyclocryotherapy, suggesting that the former may be the procedure of choice in patients for whom cyclodestructive surgery is thought to be indicated.[1-4] The 1,064-nm wavelength of the Nd:YAG laser appears to provide a suitable balance between scleral penetration and absorption by melanin in the ciliary epithelium, which are prerequisites for successful transscleral cyclophotocoagulation.[5] Histologic studies, however, suggest that the nature of the laser-induced lesion in the ciliary body is influenced by the duration of exposure of each Nd:YAG laser application.[6-8] The optimum duration has yet to be established for this operation.

To gain a better understanding of the dynamic events within the eye during various forms of transscleral Nd:YAG laser cyclophotocoagulation, and specifically to evaluate the influence of exposure duration on tissue response, we used a modification of our previously described high-magnification videographic system[9] to compare the real-time effects of three Nd:YAG lasers with varying exposure times in human autopsy eyes. To provide a histologic correlate of the videographic observations, we also compared the gross and light microscopic appearance of tissue responses to the same three lasers in a separate series of human autopsy eyes.

Material and Methods

Videographic study—Five phakic human autopsy eyes from three donors with moderate

uveal pigmentation and no history of ocular disease or prior surgery were used within 24 to 48 hours of enucleation. Each globe was trimmed of adherent conjunctiva, fat, and extraocular muscles and cemented with cyanoacrylate glue to a Plexiglas ring (40 mm outer diameter, 20 mm inner diameter opening) so that the anterior segment with several millimeters of sclera protruded through the ring. The posterior segment was cut flush to the back surface of the ring with scissors and removed, leaving the anterior vitreous and lens intact in the remaining anterior segment. A clear Plexiglas plate was placed over the cut portion of the eye and secured to the ring with a watertight sealant. Care was taken to avoid trapping air bubbles in the vitreous. This autopsy-eye mounted apparatus allowed an unobstructed view of the lens and ciliary body through the vitreous from the posterior side of the plate. Fluid volume was replaced as needed with an infusion of balanced salt solution through a 30-gauge needle inserted through the sclera into the vitreous cavity. An infrared filter was taped over the Plexiglas plate before videographic photography to prevent overexposure of the videographic image during laser applications.

As previously described, the videographic recording apparatus consisted of a long-distance microscope mounted on a portable slit lamp to give parfocal illumination.[9] A black-and-white, high-resolution videographic camera, mounted on a 32-mm objective at the microscope, was connected to a videographic monitor and recorder to capture images at a magnification of ×90 from the posterior side of the eye during laser treatment. The hemisected autopsy eye platform was securely attached to the headrest of the slit lamp.

Three Nd:YAG lasers (wavelength: 1,064 nm) were used in the study: GLase 106 (Sunrise Technologies, Fremont, California); Microruptor 2 (Lasag Medical Lasers, Thun, Switzerland); and Microruptor 3 (Lasag Medical Lasers, Thun, Switzerland).[10]

The GLase 106 is a contact, pulsed Nd:YAG laser. It delivers energy through a bare quartz fiberoptic contact probe with a tip diameter of 390 μm. It has the shortest duration of the three lasers studied with a fixed pulse duration of 0.75 millisecond, and can deliver one to ten pulses per burst. We evaluated one, five, and ten pulses per burst at energy settings of 0.4 to 0.7 J, giving calculated total energies of 0.1 to 7.0 J per lesion (133 to 933 W). Laser lesions were placed with the anterior edge of the probe either at the corneoscleral limbus or 1.0 to 1.5 mm from the corneoscleral limbus, with probe orientation either parallel to the visual axis or perpendicular to the sclera.

The Microruptor 2 is a noncontact, pulsed Nd:YAG laser with energy delivery through the slit lamp. It has a fixed pulse duration in the thermal mode of 20 milliseconds. A maximum offset between aiming and therapeutic beams of 9 (equivalent to 3.6 mm in air) was used in the study with energy settings of 4.5, 7.6, and 9.1 J per lesion (225, 380, and 455 W, respectively). The laser applications were oriented parallel to the visual axis and 1.0 to 1.5 mm from the visible corneoscleral limbus using the etch marks on a Shields transscleral cyclophotocoagulation lens (Ocular Instruments, Bellevue, Washington).

The Microruptor 3 is a continuous-wave Nd:YAG laser capable of contact or noncontact energy delivery. We evaluated only the contact method, which uses a fiberoptic probe with a 600-μm diameter quartz tip. Pulse duration is variable from 50 to 2,000 milliseconds, and laser power can be varied from 0.3 to 10 W per pulse. We used 6, 8, and 10 W at 700 and 2,000 milliseconds, giving calculated energies of 4.2 to 20.0 J per lesion. Probe position and orientation were the same as those described for the GLase 106. With both contact lasers, the handheld probe was gently pressed against the sclera.

Histologic study—Human autopsy eyes were obtained from eye banks and used within 48 hours of enucleation. These were not the same ones use in the videographic study. After removing conjunctiva, transscleral cyclophotocoagulation lesions were applied with each of the three Nd:YAG lasers, using distances from the corneoscleral limbus of 0.5, 1.0, and 1.5 mm. For treatment with the Microruptor 2, the eyes were mounted at the slit lamp, with the laser beam parallel to the visual axis, and the transscleral cyclophotocoagulation lens was used to measure the distances from the corneoscleral limbus. For the GLase 106 and Microruptor 3, a contact lens was used in which holes were drilled to allow passage of the laser probe tips to control position and angle of the probe. The holes were perpendicular to the sclera, and the probes were gently pressed against the sclera.

Settings for the GLase 106 were 0.75 millisecond duration, one, five, and ten pulses per burst, and an energy range of 100 to 700 mJ per pulse. For the Microruptor 2, the single-pulse

duration of 20 milliseconds was used with an energy range of 2 to 8 J and a maximum offset between the aiming and therapeutic beam focal points (3.6 mm in air). Settings for the Microruptor 3 were an exposure duration of 700 milliseconds and an energy range of 4 to 10 W.

After each laser application, the treatment site was marked on the sclera with india ink to facilitate identification in the histologic specimens. The eyes were then fixed for a minimum of 24 hours in acetate-buffered formaldehyde and then sectioned at the equator for gross examination with a dissecting microscope. Specimens of selected laser lesions were sectioned radially through the center of the lesion, processed for routine hematoxylin and eosin staining, and studied by light microscopy.

Results

Videographic observations—At settings of 0.4 to 0.6 J and one, five, or ten pulses per burst, little reaction could be seen videographically with the GLase 106 (Fig. 1). With 0.7 J and one or five pulses per burst, either no reaction or minimal tissue whitening with some pigment dispersion and the release of microscopic gas bubbles were observed. At 0.7 J and ten pulses per burst, pigment was explosively ejected from the center of the laser application and a large gas bubble formed over a craterlike defect in the ciliary body. Surrounding the crater was a faint ring of tissue whitening. However, there was considerable variation in the lesions at the higher settings.

Lesions appeared to form instantaneously with the fixed 20-millisecond pulse with the Microruptor 2 (Fig. 2). At 4.5 J, a small faint white lesion developed without evidence of tissue shrinkage or pigment disruption. At 7.6 J, in addition to faint tissue whitening, there was slight shrinkage and blister-like inward displacement of the epithelium, and the release of a small amount of pigment and microscopic gas bubbles into the vitreous. At 9.1 J, there was explosive disintegration of the ciliary epithelium associated with the release of a large gas bubble and production of a transillumination defect at the site of laser impact. With the 9.1-J energy, the edges of the epithelial defect were whitened and turned up at the periphery, with complete loss of the central epithelium.

At settings of 700 milliseconds and 6 W, significantly more tissue whitening and shrinkage of the ciliary body toward the center of the lesion was observed with the Microruptor 3 (Fig. 3) compared with the two pulsed lasers. At 700 milliseconds and 8 W, a slightly whiter lesion with prominent tissue shrinkage developed. At 2,000 milliseconds and 8 W, an intensely white lesion formed, associated with marked shrinkage of the ciliary processes away from the lens equator and collapse of the spaces between processes. Occasionally at the higher energy settings (8 to 10 W and 700 or 2,000 milliseconds), there was an explosive tissue disintegration associated with the release of gas bubbles and an audible pop. These explosive lesions occurred most frequently with the probe in the perpendicular orientation as discussed below. Lesion diameters at 2,000 milliseconds were approximately 50% larger than at 700 milliseconds.

The internal location of lesions for a given external placement of the laser beam was comparable among the three lasers. For lesions placed 1.0 to 1.5 mm from the corneoscleral limbus with the beam parallel to the visual axis,

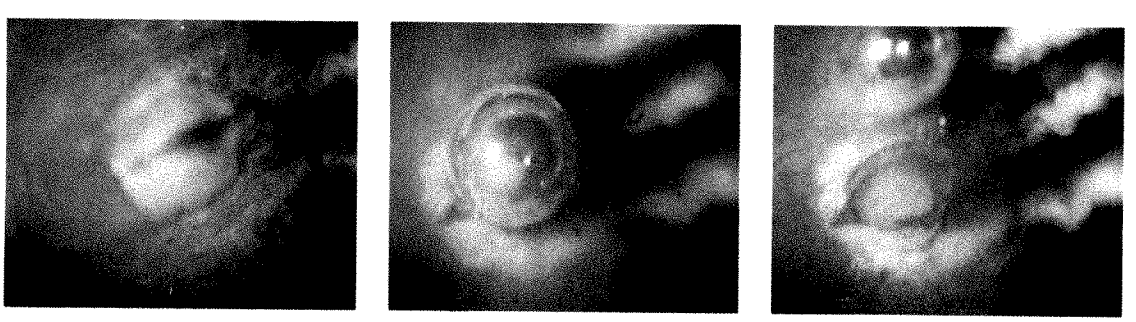


Fig. 1 (Prum and associates). Example of GLase 106 lesions (0.75-millisecond pulses) with 0.7 J and ten pulses per burst, and probe 1.0 to 1.5 mm from the corneoscleral limbus and parallel to the visual axis. After one pulse, note blister of epithelial detachment (left) followed by the release of a gas bubble that enlarges with each pulse (center), producing a crater in the pars plana surrounded by a thin rim of tissue whitening (right).



Fig. 2 (Prum and associates). Examples of Microruptor 2 lesions (20-millisecond pulses) with aiming beam 1.0 to 1.5 mm from the corneoscleral limbus and parallel to the visual axis. With 4.5 J, a faint white lesion (arrows) is apparent at the posterior border of the ciliary processes (left). With 7.6 J, there is an increase in lesion diameter compared to that created with 4.5 J (center). With a 9.1-J lesion, note crater in epithelium and a transillumination defect (right).

internal lesions typically formed within the pars plana immediately adjacent to the ciliary processes or less frequently, within the posterior slope of the processes, depending on the relative position of the ciliary body to the corneoscleral limbus in each eye studied. With beam orientation perpendicular to the sclera with the two contact lasers, lesions consistently formed closer to the posterior slope or apex of the processes. With the anterior edge of either contact probe touching the corneoscleral limbus and oriented parallel to the visual axis, lesions consistently formed in the mid-portion or posterior slope of the ciliary processes, but never in the pars plana. With the probe perpendicular to the sclera and adjacent to the corneoscleral limbus, lesions formed in the base of the iris, frequently producing clouds of dispersed pigment and visible iris transillumination defects. Occasional whitening of the lens equator was observed at the highest energy setting of the Microruptor 3.

Histologic observations—With the GLase 106, no lesion was seen grossly with one pulse per burst at any energy level. With five and ten pulses per burst, lesions were observed in the ciliary epithelium with all energies studied. These lesions were characterized grossly and histologically by extensive epithelial disruption, which we referred to as explosive-like lesions, with full-thickness holes and loss of tissue in many cases (Fig. 4).

With the Microruptor 2, no lesion was observed grossly with treatment at 2 J, but lesions were seen grossly and histologically with energy levels of 4, 6, and 8 J. These lesions were characterized by moderate to extensive tissue disruption. The typical histologic appearance was called a blister-like lesion, in which the epithelium remained intact, but was thinned and elevated from the underlying stroma (Fig. 5). Some lesions, however, did have full-thickness holes in the epithelium, which was more common with the higher energy levels.

With the Microruptor 3, lesions were observed grossly and histologically with powers

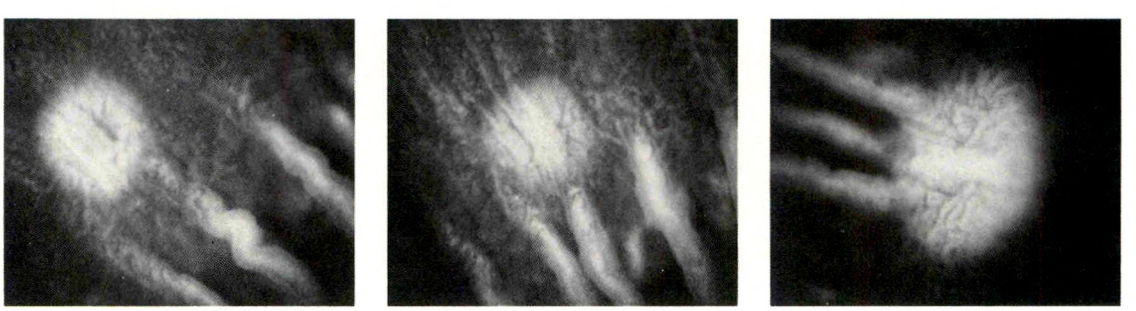


Fig. 3 (Prum and associates). Examples of Microruptor 3 lesions (continuous-wave). Using 6 W and 700 milliseconds, with a probe 1.0 to 1.5 mm from the corneoscleral limbus and parallel to the visual axis, note markedly more whitening of tissue than with pulsed lasers (left). With same parameters, but probe oriented perpendicular to sclera, note that lesion is closer to posterior slope of ciliary processes (center). With 8 W, 2,000 milliseconds, 1.0 to 1.5 mm from the corneoscleral limbus and parallel orientation, note increase in diameter of lesion compared with that created by 6 W and 700 milliseconds (right).



Fig. 4 (Prum and associates). Light microscopic appearance of explosive-like cyclophotocoagulation lesion created with GLase 106 Nd:YAG laser at 0.75 millisecond, ten pulses per burst, and 0.5 J of energy per burst, with probe oriented perpendicular to the sclera and 1 mm posterior to the corneoscleral limbus, showing marked disruption of ciliary epithelial layers (arrows) and thin layer of coagulation of underlying stroma (hematoxylin and eosin, × 40).

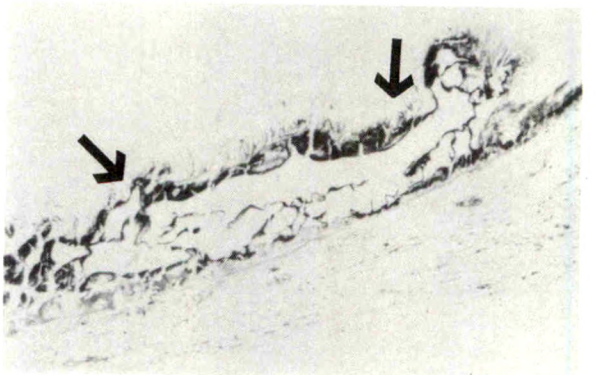


Fig. 5 (Prum and associates). Light microscopic appearance of blister-like cyclophotocoagulation lesion created with Microruptor 2 Nd:YAG laser with beam parallel to the visual axis and 1.5 mm posterior to the corneoscleral limbus and using single 20-millisecond pulse, 4 J, and maximum offset of 9. Note disruption of nonpigmented and pigmented ciliary epithelial layers (arrows) with elevation from underlying stroma and small amount of coagulation changes in stromal tissue (hematoxylin and eosin, × 40).

of 6 through 10 W. These lesions differed considerably from those created by the two pulsed Nd:YAG lasers, in that there was relatively moderate disruption but marked puckering or convolution of ciliary epithelium, with prominent coagulative changes of the underlying stroma, which we referred to as a shrinkage-like lesion (Fig. 6).

There was some degree of overlap in the videographically and histologically observed responses to all three Nd:YAG laser treatments. Lesions with the GLase 106 did not have marked epithelial disruption and full-thickness hole formation in all cases, whereas some lesions created by the Microruptor 3 did have small areas of epithelial disruption and hole formation. In general, however, there was a clear trend for the shorter duration, pulsed Nd:YAG lasers to create prominent tissue disruption. The longer duration of the continuous-wave Nd:YAG laser was most often associated with shrinkage and coagulation of the ciliary epithelium and underlying stroma.

Discussion

Most ophthalmic Nd:YAG lasers, as used for capsulotomies and iridotomies, operate in the Q-switched mode with pulse durations measured in nanoseconds. These extremely short pulses create tissue disruption at the point of focus, independent of absorption by pigment. Conversely, lasers used for cyclophotocoagulation have much longer durations of exposure that produce thermal reactions, which are dependent on absorption of laser energy by pigment to create the heat that produces the tissue reaction. Within this group of lasers, however,

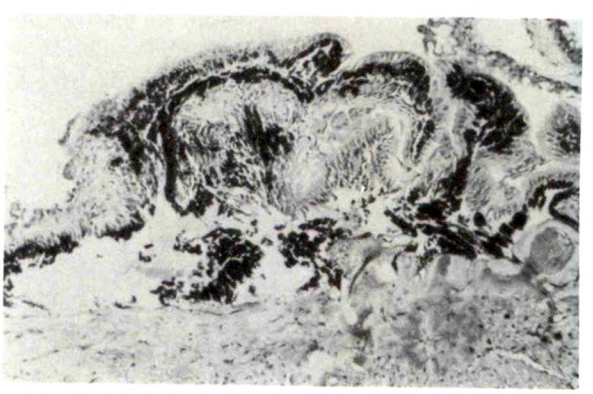


Fig. 6 (Prum and associates). Light microscopic appearance of shrinkage-like cyclophotocoagulation lesion created with Microruptor 3 at 700 milliseconds, 10 W, and probe oriented perpendicular to sclera and 1 mm posterior to the corneoscleral limbus. Note the moderate disruption and marked convolution of the two ciliary epithelial layers with slight separation from underlying stroma and prominent coagulative changes of the stromal tissue (hematoxylin and eosin, × 40).

are those that are said to be pulsed in the thermal mode, with exposure durations in the microsecond to low millisecond range, and those referred to as continuous-wave, in which the range of exposure times is from the high milliseconds to several seconds. The intent of the present study was to compare the gross and histologic findings of transscleral cyclophotocoagulation lesions created by pulsed, thermal mode and continuous-wave Nd:YAG lasers.

The early information on tissue response to transscleral laser cyclophotocoagulation came from animal eyes,[11,12] human autopsy eyes,[5,6] and living human eyes that were subsequently enucleated.[13] More recently, Hennis and associates[14] and Assia and associates[15] reported the use of a modified Miyake posterior photographic technique to study transscleral laser lesions produced by two noncontact lasers: the Microruptor 2 Nd:YAG laser and the Microlase (Keeler Instruments, Broomall, Pennsylvania) continuous-wave diode laser (wavelength, 780 to 830 nm). Assia and associates[15] described tissue whitening, bubble formation, pigment dispersion, and hole formation with the Microruptor 2, similar to our results. In the studies of Hennis and associates[14] and Assia and associates,[15] the description of lesions with the diode laser was similar to our observations with the Microruptor 3. In both reports,[14,15] 35-mm still photographs were used to illustrate observations with the Miyake system. In contrast, all illustrations in our study were taken from high-resolution black-and-white videographic images recorded during laser applications. In this way it was possible to illustrate the moment-by-moment dynamic tissue responses observed during laser applications, which are difficult to capture by still photography.

At energy levels of 7 to 9 J per burst, the two pulsed lasers in our study frequently produced explosive tissue disintegration, presumably caused by rapid heating and vapor bubble formation within the tissue. In contrast, the continuous-wave laser produced slow tissue shrinkage and whitening of the ciliary epithelium. Explosive lesions were particularly characteristic of the tissue response produced by the GLase 106, possibly related to its pulse duration of 0.75 millisecond and consequent high power output. Additionally, the smaller tip diameter of the GLase contact probe (390 μm in contrast to 600 μm with the Microruptor 3) may have concentrated the energy into a smaller area, thereby increasing the possibility of explosive tissue damage.

With both contact probe techniques, considerable variability of tissue response was observed when using a single protocol. For example, lesions produced with the Microruptor 3 at higher energy settings occasionally, but not always, produced tissue disruption with an associated audible pop. The variable responses may relate to the amount of pressure exerted by the probe against the sclera. Relatively greater pressure thins the adjacent sclera and increases the amount of laser energy reaching the ciliary body.[16]

The videographic observations correlate with findings from the histologic study, in which the same three Nd:YAG lasers were used with a different set of human autopsy eyes and the cyclodestructive lesions were evaluated grossly and by light microscopy. Although overlap was observed, the shortest duration GLase 106 caused the most tissue disruption, with what we called an explosive-like lesion. The intermediate duration Microruptor 2 caused moderate tissue disruption and elevation of ciliary epithelium that we referred to as a blister-like lesion, and the longest duration Microruptor 3 caused more puckering and coagulation of tissue in a shrinkage-like lesion.

The histologic observations are consistent with previous reports of pulsed, thermal mode and continuous-wave transscleral Nd:YAG laser cyclophotocoagulation. Hampton and Shields[6] described the blister-like elevation of the epithelial layers in human autopsy eyes after transscleral Nd:YAG laser cyclophotocoagulation with the Microruptor 2, and Blasini, Simmons, and Shields[13] reported similar histologic observations in human eyes that underwent the same procedure shortly before enucleation. In contrast, Schubert[7] and Allingham and associates[8] evaluated a continuous-wave, contact Nd:YAG laser, the SLT CL60 (Surgical Laser Technologies Inc., Malvern, Pennsylvania), in human autopsy eyes, and found smaller, more coagulative lesions with less tissue disruption than was seen with the pulsed, thermal mode Nd:YAG laser.

In both the videographic and histologic studies, the internal location of laser lesions for a given external placement of the aiming beam or probe tip was similar to that described in previous reports[6,8] and did not influence the overall division of lesions into explosive-like, blister-like, and shrinkage-like lesions for the GLase 106, Microruptor 2, and Microruptor 3, respectively.

Our observations suggest an inverse relation-

ship between the likelihood of explosive tissue disintegration and duration of the laser exposure for a given energy level (energy in joules equals power in watts times duration in seconds). It is not known, however, whether an explosive or coagulative tissue response is most desirable in transscleral laser cycloablation. In clinical trials of transscleral Nd:YAG laser cyclophotocoagulation, with the SLT CL60 at 700-millisecond duration[3] and the Microruptor 2 at 20 milliseconds,[4] the former procedure was reported to have less postoperative visual reduction. Clinical studies of pulsed, thermal mode and continuous-wave lasers have also disclosed a higher frequency of severe postoperative inflammation in patients treated with higher energy settings,[3,17] possibly because of the increased frequency of explosive tissue disintegration, as seen in our study at similar energy levels. The contact, continuous-wave lasers appear to have the advantage of producing an audible pop when the threshold between coagulation and explosive tissue disintegration is exceeded. This audible indicator provides an objective means of determining the maximum energy level that can be used to titrate the energy delivered in a given patient without incurring potentially more inflammatory explosive lesions. Additionally, the long-duration, low-wattage lesions created with the continuous-wave laser (2,000 milliseconds and 6 W) appear to have markedly larger diameters than those created with the pulsed lasers and rarely result in explosive tissue disintegration. The potential advantages of longer duration cycloablative lesions must be balanced against the possible disadvantages of greater thermal spread,[18] which may increase damage to adjacent tissue structures.

The goals for the optimum cyclophotocoagulation operation should be to maximize the effect on intraocular pressure reduction, while minimizing the risk for visual loss, inflammation, and pain. Several factors may influence the outcome of cyclophotocoagulation: the duration of laser exposure, the total energy delivered, the wavelength of the laser, the degree of tissue pigmentation, the number and location of lesions in the ciliary body, and whether the laser energy is delivered from the slit lamp or by a contact, fiberoptic probe. Our study demonstrates that the type of laser lesion produced in autopsy eyes by Nd:YAG lasers is influenced by the duration of laser exposure. Additional studies in living animals and human clinical trials will be needed to determine which type of laser lesion is optimum in meeting the clinical goals of transscleral cyclophotocoagulation.

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OPHTHALMIC MINIATURE

But on the day that Teddy came staggering into the kitchen with his fists to his eyes, shrieking with pain, Gideon dropped the pot full of hot soup that he was holding, rushed to the child, and forced aside his fingers. "A snake!" he exclaimed. Teddy had been on his scooter, and had come to a rest with his foot on the side of a big tub of plants. A tree snake, hanging by its tail from the roof, had spat full into his eyes. Mrs. Farquar came running when she heard the commotion. "He'll go blind," she sobbed, holding Teddy close against her. Gideon, he'll go blind!" Already the eyes, with perhaps half an hour's sight left in them, were swollen up to the size of fists; Teddy's small white face was distorted by great purple oozing protuberances. Gideon said: "Wait a minute, missus, I'll get some medicine." He ran off into the bush.

Mrs. Farquar lifted the child into the house and bathed his eyes with permanganate. She had scarcely heard Gideon's words; but when she saw that her remedies had no effect at all, and remembered how she had seen natives with no sight in their eyes, because of the spitting of a snake, she began to look for the return of her cook, remembering what she heard of the efficacy of native herbs. She stood by the window, holding the terrified, sobbing little boy in her arms, and peered helplessly into the bush. It was not more than a few minutes before she saw Gideon come bounding back, and in his hand he held a plant.

Doris Lessing, "No Witchcraft for Sale," *Modern British Prose*
New York, Harcourt, Brace & World, Inc., 1969, p. 180

Acquired Oculomotor, Trochlear, and Abducent Cranial Nerve Palsies in Pediatric Patients

Sylvia R. Kodsi, M.D., and Brian R. Younge, M.D.

Between January 1966 and December 1988, 160 pediatric patients (age range, 0 to 17 years) were seen at the Mayo Clinic with an acquired oculomotor (35 patients), trochlear (19 patients), abducent (88 patients), or multiple (18 patients) cranial nerve palsy. The clinical findings in the 160 pediatric patients were compared with the results obtained in other reviews of cranial nerve palsies in the pediatric age group and with the adult Mayo Clinic patients with acquired cranial nerve palsies. Trauma was the most common reason for an acquired cranial nerve palsy in our pediatric group. The percentage of patients with an acquired cranial nerve palsy resulting from trauma was significantly greater in the pediatric group (42.5%) than in adults (15.4%) ($P < .01$). The difference between the percentage of adults (15.2%) and pediatric patients (16.9%) with a cranial nerve palsy secondary to a neoplasm was not statistically significant ($P = .28$).

Several studies have reviewed acquired oculomotor, trochlear, and abducent cranial nerve palsies in the overall population.[1-8] The largest of these eight studies was from the Mayo Clinic; it consisted of four articles that reviewed more than 4,000 such cases.[1-4] Rucker,[1,2] in 1958 and 1966, reviewed 2,000 cases of acquired oculomotor, trochlear, and abducent cranial nerve palsies. Rush and Younge,[3] in 1981, reviewed an additional 1,000 cases of acquired cranial nerve palsies. The most recent series, in 1992 by Richards, Jones, and Younge,[4] reviewed over 1,000 more cases of cranial nerve palsies. Other studies of acquired cranial nerve palsies include a review of 130 patients with oculomotor nerve palsies in 1964 by Green, Hackett, and Schlezinger,[5] a review of 104 patients with abducent nerve palsies in 1960 by Shrader and Schlezinger,[6] a review of 40 acquired superior oblique muscle palsies in 1967 by Khawam, Scott, and Jampolsky,[7] and a review of 270 patients with superior oblique muscle palsies in 1986 by von Noorden, Murray, and Wong.[8]

Few reviews of acquired oculomotor, trochlear, and abducent cranial nerve palsies in the pediatric population exist.[9-12] These studies include a review by Harley[9] in 1980 of 121 pediatric patients seen at Wills Eye Hospital and St. Christopher Children's Hospital with oculomotor, trochlear, abducent, and multiple cranial nerve palsies. In 32 of these 121 patients, the cranial nerve palsies were congenital. Miller,[10] in 1977, reviewed 30 cases of oculomotor nerve palsies in pediatric patients seen at the Wilmer Institute. Thirteen of these patients had congenital oculomotor nerve palsies. Oculomotor cranial nerve palsies in pediatric patients were reviewed by Keith[11] in 1987. He described 28 cases of oculomotor nerve palsies in pediatric patients, eight of which were congenital or caused by birth trauma. Another major study of cranial nerve palsies in children, by Robertson, Hines, and Rucker[12] in 1970, reviewed 133 acquired abducent cranial nerve palsies in pediatric patients seen at the Mayo Clinic.

We undertook a large study of acquired cranial nerve palsies in pediatric patients. We analyzed the significance of our findings and compared them with the findings in other reviews of acquired cranial nerve palsies in the pediatric population and with the findings in the adult population of Mayo Clinic patients with acquired cranial nerve palsies.

Material and Methods

The previous studies by Rush and Younge[3] in 1981 and Richards, Jones, and Younge[4] in 1992

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From the Department of Ophthalmology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. This study was supported in part by Research Grant EY08039 from the National Institutes of Health.

Reprint requests to Brian R. Younge, M.D., Mayo Clinic, 200 First St. S.W., Rochester, MN 55905.

provided 2,278 consecutive cases of oculomotor, trochlear, and abducent cranial nerve palsies in the overall population. These patients were seen at the Mayo Clinic between January 1966 and December 1988 and were identified by a computer search of the Mayo Clinic diagnostic index.

From these 2,278 cases, all cases of congenital palsies, cases with incomplete data, cases of Möbius' syndrome, and cases of birth injuries were excluded. Of the remaining 1,975 cases of acquired cranial nerve palsies, all patients older than 17 years were excluded. The remaining 160 patients had oculomotor, trochlear, abducent, and multiple cranial nerve palsies and their ages ranged from 0 to 17 years. Eleven of these 160 patients had incomplete follow-up; however, we included them in our analysis because the initial information obtained was valuable. These 160 pediatric patients constituted 8% of the overall population of patients with acquired cranial nerve palsies. Associated clinical signs varied among patients; some had no other systemic or neurologic abnormality, whereas others had multiple systemic or neurologic impairments. Both inpatients and outpatients were included in our study group.

For patients who did not return to the Mayo Clinic, follow-up information was obtained either by letter or telephone.

Results

Of the 160 patients in this study, 95 (59.4%) were male and 65 (40.6%) were female. The mean age of this group was 9.4 years (standard deviation, 5.0 years). The distribution of types of palsies was as follows: oculomotor cranial nerve palsy, 35 patients (21.9%); trochlear cranial nerve palsy, 19 patients (11.9%); abducent cranial nerve palsy, 88 patients (55.0%); and multiple cranial nerve palsies, 18 patients (11.3%). The multiple cranial nerve palsies included combinations of cranial nerve palsies (oculomotor and trochlear; oculomotor and abducent; trochlear and abducent; and oculomotor, trochlear, and abducent). Abducent cranial nerve palsy was most commonly diagnosed (55% of all the cases). Bilateral involvement was most frequent among the patients with abducent cranial nerve palsies; it was seen in 17 of the 88 patients (19.3%). Only three of the 35 patients (8.6%) with oculomotor cranial nerve palsies and three of the 19 patients (15.8%) with trochlear cranial nerve palsies had bilateral involvement.

Among the causes of acquired cranial nerve palsies in our pediatric population, the most common was trauma; 68 of the cases (42.5%) were subsequent to trauma. The other causes, in descending order of frequency, were neoplasm in 27 cases (16.9%), undetermined in 23 cases (14.4%), postoperative cause in six cases (3.8%), meningitis in five cases (3.1%), hydrocephalus in four cases (2.5%), ophthalmoplegic migraine in three cases (1.9%), and viral infection in three cases (1.9%). In 21 other cases (13.1%), the acquired cranial nerve palsies were associated with 15 different diagnoses; no single diagnosis was responsible for more than two cases. The various diagnoses included aneurysm, multiple sclerosis, carotid-cavernous sinus fistula, subarachnoid hemorrhage, pseudotumor cerebri, Leigh's disease, arteriovenous malformation in the brain, postmeasles vaccination, superior sagittal sinus thrombosis, leukemia (grouped separately in previous studies of acquired cranial nerve palsies in children), Gradenigo's syndrome, orbital cellulitis with a cavernous sinus thrombosis, sinus disease, benign recurrent abducent nerve palsy, and a mesencephalic cyst.

When the causes of acquired cranial nerve palsy were analyzed by the cranial nerve affected, the most frequent explanation was trauma, regardless of the cranial nerve affected (Table 1). The three major causes of an oculomotor cranial nerve palsy, from most to least common, were trauma, undetermined, and neoplasm. Among patients with a trochlear nerve palsy, the major causes were trauma, undetermined, and other. In patients with an abducent nerve palsy, the main causes were trauma, neoplasm, and undetermined. In patients with multiple cranial nerve palsies, the main causes were trauma, neoplasm, and aneurysm.

Ipsilateral pupil abnormalities occurred in the patients with oculomotor cranial nerve palsies and multiple cranial nerve palsies. Abnormalities detected included a dilated pupil, a nonreactive pupil to light or accommodation, or a pupil that had aberrant regeneration. Among the 35 patients with an oculomotor cranial nerve palsy, 21 (60.0%) had abnormal pupils. Two of these patients had evidence of aberrant regeneration involving the pupil. Of the 18 patients with multiple cranial nerve palsies, ten (55.6%) had abnormal pupils, but none of them had aberrant regeneration of the pupillary fibers.

TABLE 1
CAUSES OF ACQUIRED CRANIAL NERVE PALSIES IN 160 PEDIATRIC PATIENTS AGED 0 TO 17 YEARS, BY AFFECTED NERVE

	CRANIAL NERVE							
	OCULOMOTOR (N=35)		TROCHLEAR (N=19)		ABDUCENT (N=88)		MULTIPLE (N=18)	
CAUSE	NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)
Trauma	14	(40.0)	7	36.8	37	(42.0)	10	(55.6)
Neoplasm	5	(14.3)	1	5.3	18	(20.5)	3	(16.7)
Undetermined	6	(17.1)	4	21.1	13	(14.8)	0	—
Postoperative cause	3	(8.6)	1	5.3	1	(1.1)	1	(5.6)
Meningitis	1	(2.9)	1	5.3	2	(2.3)	1	(5.6)
Hydrocephalus	0	—	2	10.5	2	(2.3)	0	—
Ophthalmoplegic migraine	3	(8.6)	0	—	0	—	0	—
Viral infection	0	—	0	—	3	(3.4)	0	—
Aneurysm	0	—	0	—	0	—	2	(11.1)
Other	3	(8.6)	3	15.8	12	(13.6)	1	(5.6)

The mean age of the patients without neoplasm (9.7 years; standard deviation, 4.9 years) was not significantly different from the age of the patients with a neoplasm (8.3 years; standard deviation, 5.0 years) ($P = .20$). Thirty-three of the 160 patients (20.6%) had a neoplasm. Of these 33 patients, four sustained a cranial nerve palsy as a result of neurosurgical intervention. A brainstem glioma, the most common neoplasm, was present in 12 of the 33 patients (36.4%). Other neoplasms included four metastatic tumors, three cerebellar astrocytomas, two ependymomas, two meningiomas, two craniopharyngiomas, and two cases of leukemia. The remaining neoplasms were of various types, and no specific tumor type contributed to a significant percentage of the total number of cases. Of the 31 solid neoplasms, 12 were supratentorial and 19 were infratentorial.

The frequency of neoplasms was greatest in the group of patients with abducent nerve palsies (23.9%; 21 of 88 patients), followed by multiple cranial nerve palsies (22.2%; four of 18 patients), oculomotor nerve palsies (20.0%; seven of 35 patients), and trochlear nerve palsies (5.3%; one of 19 patients). Brainstem gliomas were most often associated with an abducent cranial nerve palsy. Seven of the 12 patients with a brainstem glioma had an abducent cranial nerve palsy.

Recovery status was determined in 149 of the 160 patients (93.1%). Of these 149 patients, 54 (36.2%) did not recover, 74 (49.7%) completely recovered, and 21 (14.1%) partially recovered. Therefore, 95 of the 149 patients (63.8%) with a known recovery status had either partial or full recovery. The patients with an acquired cranial nerve palsy as a result of trauma had the highest recovery rate; 31 of 68 patients (45.6%) obtained complete recovery, and 45 of 68 patients (66.2%) obtained either partial or complete recovery. Recovery occurred less often in the patients with a cranial nerve palsy of an undetermined origin; 11 of 23 patients (47.8%) had complete recovery. Patients with neoplasms had the lowest recovery rates; only ten of 27 patients (37%) had complete recovery and 12 of 27 patients (44.4%) had either partial or complete recovery.

When recovery was analyzed according to cranial nerve involvement, complete recovery was most frequent in patients with an abducent cranial nerve palsy (54 of 88 cases; 61.4%) and least frequent in those with an oculomotor cranial nerve palsy (eight of 35 cases; 22.9%). Recovery was complete in six of the 19 patients (31.6%) with an acquired trochlear cranial nerve palsy and in six of the 18 patients (33.3%) with acquired multiple cranial nerve palsy. Recovery time was determined in 77 of the 95 patients who had partial or complete recovery. In this group, the mean recovery time was 2.3 months (standard deviation, 2.0 months). Recovery time according to the affected cranial nerve was not statistically different among the patients ($P = .63$).

Discussion

We compared acquired cranial nerve palsies in our group of pediatric patients with acquired palsies in adult Mayo Clinic patients. The adult population included 1,815 patients 18 years or older with an acquired cranial nerve palsy who were seen at the Mayo Clinic from January 1966 until December 1988. Data were obtained from the previous studies by Rush and Younge[3] and Richards, Jones, and Younge.[4]

The causes of acquired cranial nerve palsies in these 1,815 patients were categorized as undetermined, trauma, neoplasm, vascular/diabetic, aneurysm, and others. For comparison, the causes in our 160 pediatric patients were classified into these same groups (Table 2). The percentage of patients with a cranial nerve palsy secondary to trauma was significantly greater in pediatric patients (42.5%) than adults (15.4%) ($P < .01$). The percentage of adults with cranial nerve palsies caused by a neoplasm (15.2%) was not significantly different from that in pediatric patients (16.9%) ($P = .28$). Although a cause for a cranial nerve palsy is much more likely to be discovered in a pediatric patient than in an adult, a large percentage of pediatric patients (14.4%) had a cranial nerve palsy of an undetermined origin. Previous studies have reported fewer pediatric patients with a cranial nerve palsy of uncertain cause.[9,10,12]

The proportions of cases involving acquired oculomotor and multiple cranial nerve palsies in the pediatric group were similar to those in the adult population (Table 3). Oculomotor cranial nerve palsies constituted 24% of the cases in the adults and 22% of the cases in pediatric patients. The smallest percentage of cases in both the adults (11%) and the pediatric patients (11%) were multiple cranial nerve palsies. Acquired abducent cranial nerve palsies occurred significantly more often in the pediatric population (55%) than in the adult population (44%) ($P < .01$). Acquired trochlear cranial nerve palsies were significantly more frequent in the adult population (21%) than in the pediatric population (12%) ($P < .01$).

Oculomotor nerve palsies—The most frequent cause of an acquired oculomotor cranial nerve palsy in the adult population (443 patients) was undetermined (108 patients, 24.4%). The other causes were vascular/diabetic (101 patients, 22.8%), trauma (61 patients, 13.8%), aneurysm (52 patients, 11.7%), and neoplasm (47 patients, 10.6%). In comparison, trauma was the most frequent cause in the pediatric population (14 of 35 cases, 40.0%) ($P < .01$). The pediatric and adult populations had no statistically significant differences in the percentage of oculomotor cranial nerve palsies caused by neoplasm ($P = .25$) or of undetermined cause ($P = .16$). Diabetes and aneurysms were not responsible

TABLE 2
CAUSES OF ACQUIRED CRANIAL NERVE PALSIES IN 1,815 ADULTS AND 160 PEDIATRIC PATIENTS

	ADULTS* (18 YEARS OLD OR OLDER)		PEDIATRIC PATIENTS (0 TO 17 YEARS OLD)		
CAUSE	NO.	(%)	NO.	(%)	P VALUE
Undetermined	488	(26.9)	23	(14.4)	< .01
Trauma	280	(15.4)	68	(42.5)	< .01
Neoplasm	275	(15.2)	27	(16.9)	.28
Vascular/ diabetic	307	(16.9)	0	—	< .01
Aneurysm	82	(4.5)	2	(1.3)	.03
Other	383	(21.1)	40	(25.0)	.12

*This group included all Mayo Clinic patients 18 years or older with an acquired cranial nerve palsy who were seen between January 1966 and December 1988. Data were obtained from the studies by Richards, Jones, and Younge[4] and Rush and Younge.[3]

TABLE 3
OCULOMOTOR, TROCHLEAR, ABDUCENT, AND MULTIPLE CRANIAL NERVE PALSIES IN 1,815 ADULTS AND 160 PEDIATRIC PATIENTS

	ADULTS* (18 YEARS OLD OR OLDER)		PEDIATRIC PATIENTS (0 TO 17 YEARS OLD)		
CRANIAL NERVE INVOLVEMENT	NO.	(%)	NO.	(%)	P VALUE
Abducent	793	(44)	88	(55)	< .01
Oculomotor	443	(24)	35	(22)	.28
Trochlear	377	(21)	19	(12)	< .01
Multiple	202	(11)	18	(11)	> .50

*This group included all Mayo Clinic patients 18 years or older with an acquired cranial nerve palsy who were seen between January 1966 and December 1988. Data were obtained from the studies by Richards, Jones, and Younge[4] and Rush and Younge.[3]

for any oculomotor nerve palsies in the pediatric patients.

To compare our group of pediatric patients with acquired cranial nerve palsies with pediatric patients in other studies of cranial nerve palsies, we disregarded all the congenital cases in the other studies. The three other studies of oculomotor cranial nerve palsies in pediatric patients were by Miller[10] (17 patients), Harley[9] (16 patients), and Keith[11] (20 patients). Although in all three studies trauma was the major cause of an acquired oculomotor cranial nerve palsy, the percentage of cases caused by trauma was much lower in Miller's and Harley's studies (25%) than in ours (40.0%).

A neoplasm was the cause of the acquired oculomotor nerve palsy in 18% of the pediatric patients in Miller's study,[10] 19% of the pediatric patients in Harley's study,[9] 5% of the pediatric patients in Keith's study,[11] and 14.3% of the pediatric patients in our study. An aneurysm was the source of two acquired oculomotor nerve palsies in Miller's study. These two cases and a case report by Gabianelli, Klingele, and Burde[13] described a solitary oculomotor palsy related to an aneurysm in a patient younger than 18 years. None of the pediatric patients in our series had a solitary oculomotor nerve palsy caused by an aneurysm. We compared the causes of an acquired oculomotor cranial nerve palsy in the patients in Miller's study,[10] Harley's study,[9] Keith's study,[11] and our study (Table 4).

TABLE 4
CAUSES OF ACQUIRED OCULOMOTOR CRANIAL NERVE PALSIES IN PEDIATRIC PATIENTS DESCRIBED IN THE LITERATURE AND IN OUR STUDY

CAUSE OF OCULOMOTOR NERVE PALSY	NO. OF PATIENTS, BY STUDY			
	MILLER[10] (1977)	HARLEY[9] (1980)	KEITH[11] (1987)	OUR STUDY (1992)
Trauma	4	4	7	14
Neoplasm	3	3	1	5
Undetermined	0	0	4	6
Ophthalmoplegic migraine	2	3	2	3
Postoperative cause	2	0	0	3
Meningitis/ encephalitis	2	1	1	1
Subdural hematoma	0	2	0	0
Viral or post–upper respiratory tract infection	2	0	3	0
Varicella-zoster virus	0	1	1	0
Aneurysm	2	0	0	0
Orbital cellulitis	0	2	0	0
Sinus disease	0	0	0	1
Mesencephalic cyst	0	0	0	1
Cyclic oculomotor nerve palsy*	0	0	0	1
Poison	0	0	1	0
Total	17	16	20	35

*Not present at birth.

Trochlear nerve palsies—In the adult population (377 patients), the most common cause for an acquired trochlear cranial nerve palsy was undetermined (132 patients, 35.0%). Trauma (108 patients, 28.7%) was the second most common cause, followed by vascular/diabetic (55 patients, 14.6%). The causes were classified as other in 63 of the 377 cases (16.7%).. Other studies[7,8,14] have identified trauma as the most common cause of an acquired trochlear cranial nerve palsy.

In the pediatric population, the most common cause of an acquired trochlear cranial nerve palsy was trauma (seven of 19 cases; 36.8%), followed by undetermined causes (four of 19 cases; 21.1%). In three of the 19 cases (15.8%), the causes were classified as other. These included one case each of Leigh's disease, subarachnoid hemorrhage, and an arteriovenous malformation in the brain. Although the frequency of trauma was higher ($P = .22$) and the frequency of undetermined causes was lower ($P = .11$) in the pediatric population than in the adult population at the Mayo Clinic, the differences were not statistically significant. Little information regarding causes of acquired trochlear cranial nerve palsies in pediatric patients exists. In Harley's review[9] of cranial nerve palsies in pediatric patients, only six patients had an acquired trochlear cranial nerve palsy, and in five of these the cause was trauma.

Abducent nerve palsies—The most common cause for an acquired abducent nerve palsy in the adult population (792 patients) was undetermined (227 patients, 28.5%), followed by neoplasm (143 patients, 18.1%), vascular/diabetic (140 patients, 17.7%), and trauma (77 patients, 9.7%). In pediatric patients with acquired abducent nerve palsies, the frequency of trauma (37 of 88 patients, 42.0%) was higher

and the frequency of undetermined causes (13 of 88 patients, 14.8%) was lower than those in the adult population ($P < .01$). Several studies have found that neoplasms are a more common cause of acquired abducent cranial nerve palsies in pediatric patients than in adults.[9,12] In our study, however, acquired abducent cranial nerve palsies were caused by a neoplasm in 18.1% of the adult population and in 20.5% of the pediatric population. This difference was not statistically significant ($P = .29$).

In 1970, Robertson, Hines, and Rucker[12] analyzed acquired abducent nerve palsies in 133 pediatric patients seen from 1952 through 1964. Robertson, Hines, and Rucker[12] found that neoplasms caused 39% of the acquired abducent nerve palsies, followed by trauma (20%), and inflammation (17%). In their study, only 9% of the acquired abducent nerve palsies were of undetermined cause. In Harley's study,[9] 57 patients had an acquired abducent nerve palsy. The causes were traumatic in 21 of the 57 patients (37%), a neoplasm in 17 patients (30%), and undetermined in four patients (7%). In our series, 42.0% of the abducent nerve palsies (37 of 88 patients) were caused by trauma and only 20.5% by neoplasm (18 of 88 patients). Despite improved neuroimaging techniques, the percentage of undetermined cases increased to 14.8% (13 of 88 patients). Therefore, there was a noticeable change in the distribution of causes of abducent cranial nerve palsies from the 1950s to the present.

A concern in a pediatric patient with an isolated acquired abducent cranial nerve palsy is that it may be the first indication of an intracranial neoplasm. We analyzed our 18 cases of an acquired abducent cranial nerve palsy caused by neoplasm to determine whether other neurologic signs or symptoms were present at the time the palsy developed. Fifteen of the 18 patients had other neurologic signs and symptoms present when the abducent nerve palsy developed. These findings included facial nerve palsies, ataxia, dysarthria, papilledema, and hemiparesis. Two of the three patients without other neurologic findings had known metastatic cancer. Only one of the 18 patients had no other neurologic signs or symptoms or previous history of metastatic cancer. This patient had a brainstem glioma, and marked ataxia and dysarthria developed two months after development of the abducent nerve palsy. In our study, the cause of an acquired abducent cranial nerve palsy was unlikely to be neoplasm if the patient had no other neurologic signs or symptoms or previous history of metastatic cancer.

Comparison of the results described by Robertson, Hines, and Rucker,[12] by Harley,[9] and in our study shows that in recent studies fewer acquired abducent nerve palsies in the pediatric population are caused by a neoplasm than in the past. A possible theory to explain the decreased frequency of abducent nerve palsies associated with neoplasms involves the development of computed tomography and magnetic resonance imaging. Most patients in our study were seen after computed tomography became available. However, at the time of the review by Robertson, Hines, and Rucker,[12] computed tomography was unavailable. Currently, in many pediatric patients with central nervous system tumors, a neurologist may make the diagnosis before the development of an abducent cranial nerve palsy as a result of other abnormalities and the easy access to excellent neuroimaging techniques. An abducent nerve palsy may still develop later in the course of disease, but the ophthalmologist may not necessarily be consulted to verify its presence in a pediatric patient with a known tumor of the central nervous system.

In the study by Robertson, Hines, and Rucker,[12] the group of pediatric patients with inflammation as the cause of their abducent cranial nerve palsy included those with meningitis and Gradenigo's syndrome. With the widespread use of antibiotics, Gradenigo's syndrome has become rare; as a result, we had a smaller percentage of patients with an acquired abducent nerve palsy attributed to inflammation. We compared the causes of an acquired abducent cranial nerve palsy in the pediatric patients described by Robertson, Hines, and Rucker,[12] by Harley,[9] and in our patients (Table 5).

Multiple cranial nerve involvement—Acquired multiple cranial nerve palsies in the adult population (201 patients) were most often caused by neoplasm (70 patients, 34.8%), followed by trauma (34 patients, 16.9%), undetermined cause (22 patients, 11.0%), and aneurysm (13 patients, 6.5%). Although the number of pediatric patients with acquired multiple cranial nerve palsies was limited, in this group trauma (ten of 18 patients, 55.6%) was a more common cause of multiple cranial nerve palsies than in the adult population ($P < .01$). Although the percentage of patients with a multi-

TABLE 5
CAUSES OF ACQUIRED ABDUCENT CRANIAL NERVE PALSIES IN PEDIATRIC PATIENTS DESCRIBED IN THE LITERATURE AND IN OUR STUDY

CAUSE OF ABDUCENT NERVE PALSY	NO. OF PATIENTS, BY STUDY		
	ROBERTSON, HINES, AND RUCKER[12] (1970)	HARLEY[9] (1980)	OUR STUDY (1992)
Trauma	26	21	37
Neoplasm	52	17	18
Undetermined	12	4	13
Viral/benign	0	3	3
Gradenigo's syndrome	7	2	1
Meningitis/ encephalitis	13	0	2
Pseudotumor cerebri	5	2	1
Leukemia	2	2	2
Hydrocephalus	6	0	2
Arteriovenous malformation, brain	1	0	1
Multiple sclerosis	0	1	2
Miscellaneous	9*	5†	6‡
Total	133	57	88

*One case each of abscess, spontaneous subdural hematoma, lateral ventricle cysts, and Gaucher's disease; two cases were caused by cerebellitis, and three were caused by aneurysms.

†One case each of dermatomyositis, varicella-zoster virus, Tolosa-Hunt syndrome, lead poisoning, and orbital pseudotumor.

‡One case each caused by a postoperative cause, measles vaccine, superior sagittal sinus thrombosis, and benign recurrence; two cases were caused by carotid-cavernous sinus fistulas.

ple cranial nerve palsy caused by a neoplasm was greater in adults than in pediatric patients, this difference was of borderline statistical significance ($P = .06$). The percentage of cases in both the pediatric and the adult population attributed to aneurysms was similar and not statistically different ($P = .23$).

Aneurysms in the pediatric population are rare, and the only two patients with aneurysms in our study had multiple cranial nerve involvement. Both patients had other neurologic signs and symptoms suggestive of an aneurysm.

Harley[9] described nine pediatric patients with multiple acquired cranial nerve palsies (four had orbital inflammation, three had trauma, and two had a neoplasm as the cause of the palsy).

Because the challenge of acquired cranial nerve palsies in pediatric patients differs from that in adult patients, we hope this review will guide ophthalmologists in the differential diagnosis of an acquired cranial nerve palsy in pediatric patients.

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Development of Object Vision in Infants With Permanent Cortical Visual Impairment

Teresa C. Chen, B.S., Margot H. Weinberg, B.S., Robert A. Catalano, M.D., John W. Simon, M.D., and William A. Wagle, M.D.

We examined 30 infants in whom cortical visual impairment was diagnosed during their first year of life to ascertain prognostic factors for the development of object vision, defined as the ability to recognize faces or hand-held toys. All patients were followed up for a minimum of 12 months. The most common causes of cortical visual impairment in the 30 infants were hydrocephalus in nine infants (30.0%), birth asphyxia or neonatal hypoxia in eight infants (26.7%), intracranial hemorrhage with or without hydrocephalus in seven infants (23.3%), and meningitis in five infants (16.7%). Lack of development of object vision was associated only with hypoxia (P = .013). Findings on ophthalmic examination, an abnormality in the visual pathway on computed tomographic or magnetic resonance scan, and seizures, hydrocephalus, intracranial hemorrhage, meningitis, cerebral palsy, developmental delay, prematurity, microcephaly, and hearing deficit, did not appear to be risk factors for the lack of development of object vision.

CORTICAL VISUAL IMPAIRMENT results from bilateral postchiasmatic cerebral lesions. Infants with cortical visual impairment have poor vision, absent optokinetic nystagmus, normal pupillary reflexes, and normal ocular structure. Common causes in infants include meningitis,[1-7] cerebral hemorrhage,[2,4,7-10] hypoxia,[1,3,4,7,10-13] hydrocephalus,[1,2,7-9,14] and head trauma.[3,4,7,8,15,16] Frequent associations include epilepsy,[2,3,8,9,17,18] microcephaly,[2,8] mental retardation,[8,9] and premature birth.[1] The diagnosis can usually be confirmed by an intact electroretinogram and an abnormal visual-evoked potential mapping.[16]

Although infants with cortical visual impairment seldom develop vision adequate for sighted education,[19] some develop object vision, the ability to recognize objects as small as faces or hand-held toys. Children who do not develop object vision have at most a perception of light and dark.

Electroencephalograms and visual-evoked potentials have not been useful in predicting visual recovery.[5,18,19] Computed tomographic and magnetic resonance findings of abnormal optic radiations, however, have been suggested as prognosticators.[14,18] It has also been suggested that certain associated findings are good prognostic signs for the development of object vision. Epilepsy, microcephaly,[2] stroke,[18] or bacterial meningitis[19] has been associated with poorer prognosis. Nonvascular or surgical causes; associated hypertension or diabetes[18]; nystagmus[2]; and absence of cognitive, language, or memory deficits have all been associated with a better prognosis.[18]

Other investigators described transient cortical visual impairment,[11,15,17] cortical visual impairment in adults,[6,20,21] or computed tomographic and magnetic resonance scans as prognosticators.[22] We sought to define further the clinical entity of permanent cortical visual impairment in infants and the value of computed tomographic and magnetic resonance scans as prognosticators of vision development. Associations of certain clinical features with better vision development were also studied.

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From the Departments of Ophthalmology (Mss. Chen and Weinberg, and Drs. Catalano and Simon) and Radiology (Dr. Wagle), Albany Medical College, Albany, New York. This study was supported in part by grant SO7RR05394-28 from the Biomedical Research Support Grant Program, Division of Research Resources, National Institutes of Health (Dr. Catalano); and by an unrestricted grant from Research to Prevent Blindness, New York, New York.

Reprint requests to Robert A. Catalano, M.D., Olean General Hospital, 515 Main St., Olean, NY 14760.

Patients and Methods

Patient selection—A review of the records of two of us (R.A.C., J.W.S.) identified 30 infants who were between 6 and 12 months old who had sustained cortical visual impairment when they were initially examined at Albany Medical Center Hospital between 1982 and 1990, and who had a minimum follow-up of 12 months. Cortical visual impairment was diagnosed if the infant had poor vision at initial examination, absent optokinetic nystagmus, normal pupillary reflexes, and normal ocular structure. There were 13 baby boys and 17 baby girls. Infants with optic nerve atrophy were included, but those with transient cortical visual impairment, afferent pupillary defect, optic nerve hypoplasia, retinal abnormalities, and albinism were excluded.

Ophthalmic examination—All 30 infants had a complete history obtained and underwent ophthalmic examination. The presence of seizures, hydrocephalus, intracranial hemorrhage, hypoxia/asphyxia, meningitis, cerebral palsy, mental retardation, prematurity (less than 36 weeks postconceptual age at birth by Dubowitz score), microcephaly, and hearing deficits were noted by history and interview with the infant's pediatrician. The ophthalmic examination identified pupillary response, optokinetic nystagmus, exaggerated widening of the palpebral fissure on reduction of ambient illumination, and strabismus. The optic nerve and retinal abnormalities were studied with direct and indirect ophthalmoscopy and the refractive errors were measured after cycloplegia.

Developmental and radiologic testing—Developmental assessments were obtained from the infants' pediatricians. Magnetic resonance and computed tomographic scans were reviewed at Albany Medical Center by a neuroradiologist, who was not cognizant of the patients' medical histories or the extent, if any, of the patients' development of vision.

Statistical analysis—Patients were divided on the basis of the development of object vision. Significant differences between the two groups were evaluated by chi-square analysis, with Yates correction used for smaller sample sizes. Kendall's tau b correlation coefficients were also calculated in correlation analysis.

Results

Histories and developmental assessments of the 30 infants indicated developmental delay in 22 infants (73.3%), seizures in 17 infants (56.7%), cerebral palsy in ten infants (33.3%), and prematurity in nine infants (30.0%). Five infants (16.7%) had hearing deficits, and two infants (6.7%) had microcephaly. The most common perinatal association was hydrocephalus in nine infants (30.0%). Other associations included hypoxia or postnatal asphyxia in eight infants (26.7%) and intracranial hemorrhage in seven infants (23.3%). Meningitis was a postnatal association in five infants (16.7%).

Twenty-eight of the 30 infants studied (93.3%) had normal pupillary responses. Nine infants (30.0%) had nystagmus other than optokinetic, including horizontal, pendular, downbeat, and searching nystagmus. Exaggerated widening of the palpebral fissure on reduction of ambient illumination was present in 12 of the 20 infants (60.0%) in whom this was tested. Each patient was tested for strabismus; exotropia was identified in 15 infants and esotropia in three (10.0%) infants. Most patients had mild hyperopia, as expected at this age. Myopia of greater than 2 diopters was present in at least one eye in seven of the 29 infants tested (24.1%). Astigmatism, of greater than 2 diopters, was the next most common refractive error, present in at least one eye in three of the 29 patients tested (10.3%). None of the infants had hyperopia greater than 5 diopters beyond 2 years of age. Optic nerve atrophy was seen in 11 of the 30 infants (36.7%).

Neuroimaging was performed in 25 infants: 22 underwent computed tomography, one underwent magnetic resonance imaging, and two underwent both studies. An abnormality in the visual pathway was detected by computed tomography or magnetic resonance imaging in 17 of 25 infants (68%).

Object vision developed in 15 of 30 patients during a follow-up period of 12 to 95 months (mean, 43 months). Of the patients who developed object vision, computed tomography showed that cortical tissue loss was the most common finding. Diffuse tissue atrophy was present in six of 12 infants. Focal tissue loss of the occipital lobes was present in three of 12

patients (25.0%). Dysmorphic ventricles or hydrocephalus was the next most common finding, occurring in seven of 12 infants (58.3%). In three of 12 infants (25.0%), cysts were in the midline or occipital region. Results of magnetic resonance imaging of one infant were negative except for a vague diffuse midline.

Of the infants without object vision, 12 underwent computed tomography. Diffuse cortical loss was noted in five of the 12 infants (41.7%), one of whom had severe loss of left frontal-parietal-occipital regions with milder cortical atrophy of the right side. Enlargement of the ventricles was noted in five of the 12 patients (41.7%). Two of the infants who did not develop object vision underwent magnetic resonance imaging. One study showed marked hydrocephalus, diffuse severe tissue loss, and no cortex. The other study disclosed moderate atrophy with ventricular dilatation and a slightly increased periventricular white-matter signal.

The findings in infants with and without object vision were compared (Table). No statistically significant relationship between ophthalmic or radiologic findings and object vision was found, even after multivariate analysis. A history of birth asphyxia or postnatal hypoxia was associated with a poor prognosis for the development of object vision (P = .013), as was a history of seizures (P = .065). All other P values between the two groups were greater than .05 (P = .143 to .999).

TABLE

COMPARISON OF HISTORICAL, OPHTHALMIC, AND RADIOLOGIC FINDINGS IN INFANTS WITH CORTICAL VISUAL IMPAIRMENT WHO DID AND DID NOT DEVELOP OBJECT VISION

	INFANTS WHO DEVELOPED OBJECT VISION	INFANTS WITHOUT OBJECT VISION	
FINDING	NO./TOTAL	NO./TOTAL	P VALUE
Hypoxia/asphyxia	1/15	7/15	.013
Seizures	6/15	11/15	.065
Microcephaly	0/15	2/15	.143
Intracranial hemorrhage	5/15	2/15	.195
Normal visual pathway by neuroimaging	5/12	3/13	.319
Exotropia	8/15	7/15	.365
Exaggerated widening of the palpebral fissure	6/9	6/11	.582
Astigmatism > 2 diopters	2/15	1/14	.584
Myopia > 2 diopters	3/15	4/14	.590
Esotropia	2/15	1/15	.609
Meningitis	3/15	2/15	.624
Hearing deficit	2/15	3/15	.624
Hydrocephalus	5/15	4/15	.690
Prematurity	5/15	4/15	.690
Optic atrophy	6/15	5/15	.705
Nystagmus	4/15	4/15	.999
Cerebral palsy	5/15	5/15	.999
Developmental delay	11/15	11/15	.999

Discussion

Cortical blindness is commonly defined as a complete loss of vision.[8,23] We defined object vision as the ability to see large objects such as faces or hand-held toys. Because half of our study population had object vision, cortical visual impairment is a more accurate term.

Considerable evidence suggests that two visual systems may be present in humans, one of which involves object vision.[8,24,25] Object vision is associated with the macula, the lateral geniculate body, and the striate cortex, with interaction of the colliculus superior. The other visual system deals with panoramic vision and is primarily concerned with spatial relationships and movement. It is believed that this system orients the eyes and limbs to sudden movements registered by the peripheral retina. Its visual pathways include the peripheral retina, the inferior pulvinar nucleus, and cortical areas 18 and 19.[8]

Previously described cortical visual impairment diagnostic criteria were consistent with our results.[8,15,18,21] Two of our 30 patients (6.7%), however, did not have a pupillary response. A coexisting prechiasmal lesion was likely present in these patients.

Two thirds of our patients (17 of 25 patients) had abnormal results of neuroradiologic examinations. No distinctions, however, between infants with and without object vision could be made on the basis of computed tomography. In our patients, this imaging technique could not prognosticate the development of object vision.

Previous studies suggest that poor visual

prognosis may be associated with abnormalities in the optic radiations and with periventricular leukomalacia, which results from ischemic injury to periventricular watershed zones in premature infants.[14,26,27] Because magnetic resonance imaging would best show these myelination and white-matter abnormalities, a better correlation of functional recovery and radiographic findings might have been found if magnetic resonance imaging had been the standard. The only statistically significant difference between infants who did and did not develop object vision was the presence of birth asphyxia or postnatal hypoxia (P = .013). Since P values increased with Yates correction, a larger sample size may have detected other differences between these two populations.

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Ocular Findings in Cockayne Syndrome

Elias I. Traboulsi, M.D., Inge De Becker, M.D., and Irene H. Maumenee, M.D.

The ocular findings in eight patients with Cockayne syndrome included enophthalmos, hyperopia, poor pupillary dilation, and retinal dystrophy in all patients. Four patients had strabismus. Two patients had cataracts. Three patients had nystagmus. Visual acuity was relatively well preserved in six patients, including a 25-year-old man with a visual acuity of 20/60 in each eye despite advanced retinal pigmentary changes. Failure of DNA and RNA synthesis to recover after ultraviolet light exposure as well as selective loss of repair of transcriptionally active DNA may account for the ocular abnormality in this progeric syndrome.

COCKAYNE SYNDROME is an autosomal recessive condition characterized by growth retardation, a progeroid facies with a small head, disproportionately long limbs, photodermatitis, and skeletal malformations with knee contractures resulting in a horseriding stance.[1-3] In a comprehensive review of the 140 cases reported to date in the literature, Nance and Berry[4] determined that the criteria required for the diagnosis of the Cockayne syndrome are poor growth and neurologic abnormalities. Sensorineural hearing loss, pigmentary retinopathy, cataracts, cutaneous photosensitivity, and dental caries were common manifestations of the disease. Nance and Berry[4] also found that prenatal growth failure, congenital structural eye anomalies, severe neurologic dysfunction from birth, and the presence of cataracts within the first three years of life were predictors of severe disease and early death. Biochemical and genetic heterogeneity were evidenced by the wide spectrum of symptoms and severity of the disease. We have examined and followed up eight patients with Cockayne syndrome for 20 years.

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From the Johns Hopkins Center for Hereditary Eye Diseases, Wilmer Ophthalmological Institute, Johns Hopkins Hospital, Baltimore, Maryland. This study was supported in part by the Laura Krieble and the Walter Edel Funds of the Johns Hopkins Center for Hereditary Eye Diseases, and by the E. A. Baker Foundation and the Canadian National Institute for the Blind (Dr. De Becker). This study was presented at the meeting of the Association for Research in Vision and Ophthalmology, Sarasota, Florida, May 6, 1992.

Reprint requests to Elias I. Traboulsi, M.D., Wilmer Ophthalmological Institute, Maumenee 317, 600 N. Wolfe St., Baltimore, MD 21205.

Subjects and Methods

We studied five females and three males. All patients had enophthalmos. Four patients had strabismus and two had amblyopia (Patients 6 and 7 in the Table). Seven patients were hyperopic with errors of refraction measuring up to +10.00 diopters.

Results

Systemic findings were characteristic in all patients with growth retardation, progeroid facies with malar photodermatitis, and mild to moderate mental retardation (Figs. 1 and 2). Hearing loss was present in Patient 1 at age 16 years and in Patient 2 at age 1 year; audiograms were normal in Patients 6 and 7 who were siblings.

Pupillary dilation was difficult, and in most patients a pupillary diameter of 5 or 6 mm only could be achieved after the instillation of several sets of dilating agents including phenylephrine 2.5%, tropicamide 2%, and cyclopentolate 2%. The irides of Patient 1 showed peripheral radial transillumination defects (Fig. 3), and there was prominent pigment dusting over the corneal endothelium. The lenses were clear in all except two patients. Patient 3 had cortical and posterior subcapsular vacuoles bilaterally at age 12 years. Patient 8 had bilateral congenital nuclear cataracts and nystagmus at age 8 weeks. At that time the diagnosis of Cockayne syndrome had not been established. The infant

TABLE
SALIENT OCULAR FEATURES IN EIGHT PATIENTS WITH COCKAYNE SYNDROME

PATIENT NO., AGE (YRS), GENDER	VISUAL ACUITY R.E.	VISUAL ACUITY L.E.	IRIS	LENS	REFRACTION (DIOPTERS)	RETINA	ADDITIONAL ABNORMALITIES
1, M, 25	20/60	20/60	Iris cysts; transillumination at base in a radial fashion; poor dilation	Clear	Hyperopia	Optic atrophy; salt-and-pepper pigment with few bony spicules	Mental retardation, deafness, short stature
2, 1, F	Central, steady, and maintained in both eyes		Poor dilation	Clear	+6.00 both eyes	Optic atrophy; constricted retinal vessels	Cleft palate; hearing loss
3, 12, F	1/30	1/30	Poor dilation	Cortical posterior vacuoles both eyes	+10.00 both eyes	Optic atrophy; thin retinal vessels; no electroretinographic responses to bright light flash	Crowded teeth
4, 5, F	20/60	20/30	Poor dilation	Clear	Hyperopia	Pigment migration in periphery; attenuated vessels	None
5, 2½, F	Central, steady, and maintained in both eyes		Poor dilation	Clear	+6.50 both eyes	Optic atrophy; fine pigment mottling; electroretinographic amplitude reduced by one half	None
6, 7, F	20/80	20/60	Poor dilation	Clear	R.E.: +3.50 L.E.: +2.50 +1.50	No foveal reflex; tapetal reflexes; chorioretinal atrophy; normal electroretinogram	Nystagmus; basal ganglia calcified; ataxia; normal audiogram
7, 4, M	20/40	20/40	Poor dilation	Clear	R.E.: +2.00 L.E.: +4.50 +0.50	No foveal reflex; tapetal reflexes; chorioretinal atrophy; normal electroretinogram	Nystagmus; normal computed tomogram of head; normal audiogram
8, 1½, M	Light perception		Normal	Nuclear cataracts both eyes	Not done	Optic atrophy; fine pigmentary changes; attenuated retinal vessels	Nystagmus; most severely affected patient in this series

was slightly dysmorphic and there was poor growth and failure to thrive. The patient was lost to follow-up for more than one year. At that time the facial and systemic features were characteristic (Fig. 4), and we then established the diagnosis. The cataracts were extracted and ophthalmoscopy showed marked optic atrophy, attenuation of the retinal vasculature, and fine pigmentary changes involving the macula and peripheral fundus. Fine pigmentary changes were present in all patients along with a variable degree of optic atrophy; bony spicules were present only in the oldest patient. The retinal vessels were attenuated in all patients. Electroretinographic responses were absent in the two older patients and reduced to one-half normal amplitude in the 2½-year-old girl. They were normal in Patients 6 and 7 and were not recorded in the remaining patients.

Discussion

In 1936,[1] and again in 1946,[2] Cockayne described a syndrome of "dwarfism with retinal atrophy and deafness." Clinical features become evident at age 1 to 2 years and consist of cachectic and disproportionate dwarfism. Musculoskeletal changes include kyphoscoliosis, ankylosis, a horseriding stance, long limbs, and large hands and feet.[5,6] Patients are microcephalic and have a progeroid facies with lack of subcutaneous fat, prominence of the facial

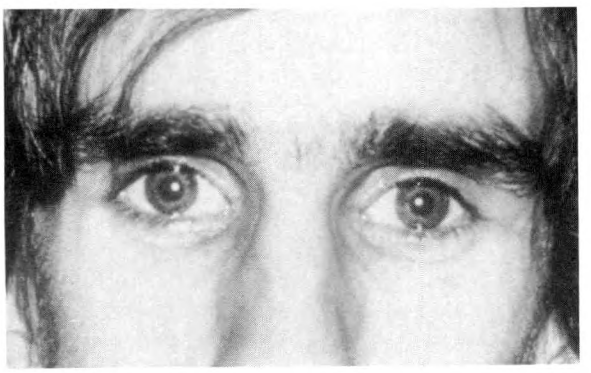


Fig. 1 (Traboulsi, De Becker, and Maumenee). Patient 1. A 25-year-old man with Cockayne syndrome and typical progeroid appearance.

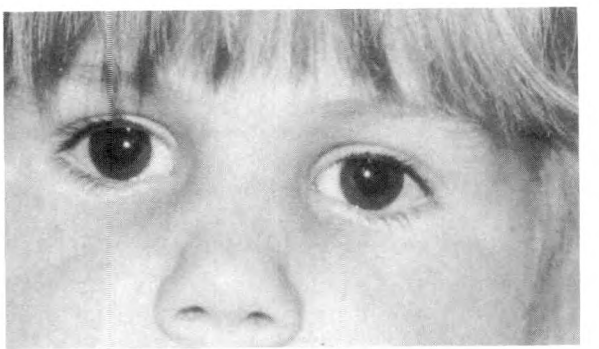


Fig. 2 (Traboulsi, De Becker, and Maumenee). Patient 5. A 2½-year-old girl with malar photodermatitis.

bones, enophthalmos, a thin often beak-like nose, large ears, and dental abnormalities. Sensorineural deafness[7] and progressive neurodegeneration with mental retardation, cerebellar ataxia, choreoathetosis, epilepsy, extrapyramidal tract signs, intracranial calcifications, and peripheral neuropathy become evident with time.[8] Photodermatitis of sun-exposed areas is a prominent feature and was present in several of our patients. When the diagnosis is suspected, parents should be questioned about the presence of facial photosensitivity. Death ensues in the second to fourth decades. There appears to be an early-onset form of Cockayne syndrome with intrauterine onset of growth retardation and evidence of clinical features at birth.[9-11] One patient with an apparent late-onset form of the disease and an interstitial deletion of the long arm of chromosome 10 [del(10)(q11.23q21.2)] was reported by Fryns and associates[12] who suggested that the gene for late-onset Cockayne syndrome is at 10q21.

When cultured fibroblasts from patients with Cockayne syndrome are exposed to ultraviolet-C light, there is defective recovery of DNA and RNA replication, but no increase in chromosomal breakage or abnormalities in DNA repair such as those seen in xeroderma pigmentosum and Bloom syndrome.[13-15] There is, however, an inability to repair transcriptionally active DNA.[16] Venema and associates[16] postulated that neurodegeneration in Cockayne syndrome may be associated with the preferential loss of repair of active genes and is not simply correlated with reduced levels of overall repair. Genetic heterogeneity has been demonstrated in the Cockayne syndrome and three complementation groups have been identified to date.[17,18] There are no reports of an increased incidence of cancer in patients with Cockayne syndrome.[4,19] The failure of RNA synthesis to recover after exposure to ultraviolet light has been used for antenatal diagnosis.[20] Patients

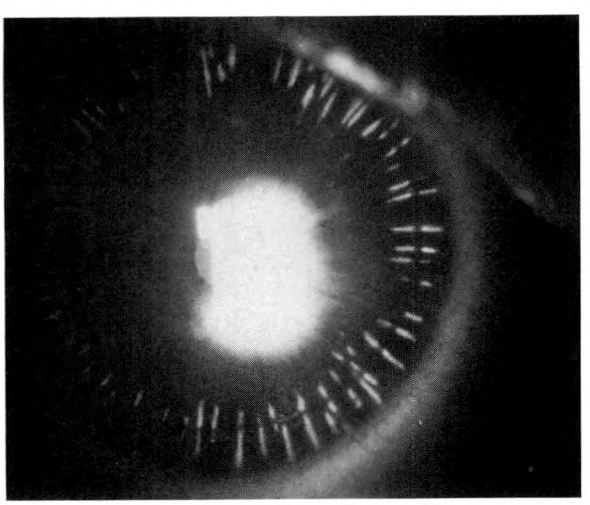


Fig. 3 (Traboulsi, De Becker, and Maumenee). Patient 1. Peripheral iris transillumination defects.



Fig. 4 (Traboulsi, De Becker, and Maumenee). Patient 8. Congenital nuclear cataracts in a 15-month-old boy with Cockayne syndrome.

may have hyperbetaglobulinemia, hyperinsulinemia, and hyperlipoproteinemia. The differential diagnosis of Cockayne syndrome includes Bloom syndrome, Rothmund-Thompson syndrome, xeroderma pigmentosum, and progeria.

Enophthalmos is present in all patients and is caused by loss of subcutaneous and orbital fat. Visual acuity was surprisingly well preserved in most of our patients in the face of advanced optic atrophy and retinal dystrophic changes; the oldest patient maintained a visual acuity of 20/60 in both eyes to the age of 25 years. He started having difficulties with night vision in the third decade of life. Visual acuity could not be measured in Patient 8 who had congenital cataracts, but it was probably markedly reduced as evidenced by the presence of nystagmus and the inability of the patient to fixate at or follow even large targets. Exotropia was present in Patient 3. Esotropia was present in Patients 2, 6, and 7. The cause of the esotropia and the presence or absence of any associated amblyopia could not be determined clinically. The ocular deviation persisted despite wearing the appropriate hyperopic correction. Nystagmus is rare in the Cockayne syndrome and was present in six of 46 previously described patients[21] and in three of our patients (Patients 6 through 8). Nystagmus may be caused by early visual deprivation from cataracts or severe retinal dystrophy, as in our Patient 8, or from central nervous system dysfunction, as we postulate in our Patients 6 and 7. An apparently consistent ocular finding in Cockayne syndrome is the poor pupillary response to dilating agents; several sets of different mydriatic and cycloplegic agents were instilled in our patients' eyes with only moderate mydriasis; one possible explanation for the poor dilation is atrophy of the dilator muscle fibers as evidenced by peripheral iris transillumination defects in our oldest patient (Patient 1); however, even the youngest patient's pupils (Patient 2) dilated poorly. The presence of pigment dispersion in the anterior segment of the oldest patient in this series indicates an either mechanical, light-toxic, or degenerative process involving the iris and resulting in atrophy and poor pupillary dilation. Pigment dispersion in the anterior and posterior chambers has been documented histopathologically by Levin and associates.[22] Raised inferior corneal lesions, band keratopathy, and recurrent erosions have been described in patients with Cockayne syndrome[23,24] but were not present in any patient in the present series; these changes may be the result of corneal exposure in neurologically impaired patients or may represent a specific feature of this condition. Cataracts have been described in about 15% of patients[21] and were present in both of Cockayne's original patients.[1,2] Nance and Berry[4] believed cataracts that develop in the first three years of life are predictors of poor outcome for longevity. We observed bilateral mild cortical and posterior subcapsular vacuolization in Patient 3 and congenital nuclear cataracts in Patient 8, one of the more severely affected patients whom we have examined. All of our patients had hyperopic errors of refraction as high as +10.00 diopters, as reported previously.[21]

Pigmentary retinopathy is one of the most consistent physical features of the Cockayne syndrome. The pigmentary changes were fine and involved mostly the peripheral fundus. Patients have been described who lacked the typical fine pigmentary changes and who exhibit denser black pigmentation in the posterior pole.[23] Bony spicules were only present in the oldest patient in our series (Patient 1), indicating that they are more advanced signs of the retinal dystrophy in this disease. There is a variable degree of reduction of scotopic and photopic electroretinographic responses, most severe in older patients, as was the case in our series. The electroretinograms were normal in Patients 6 and 7, who had the mildest retinal dystrophic changes. We believe that genetic heterogeneity, as evidenced by at least three complementation groups, is the cause of the variability in retinal dystrophic and functional changes in our patients. Retinal dystrophy or decreased electroretinographic responses, or both, are required diagnostic criteria for Cockayne syndrome. Nance and Berry[4] found retinal dystrophy in only 60% of their patients and stated that the minimal diagnostic criteria were growth retardation and neurologic deficits. Our eight patients met the above criteria and all had retinal dystrophy and progeroid appearance. Loss of subcutaneous fat may not be prominent in younger patients, as illustrated in Figures 2 and 4.

Ocular histopathologic findings in one patient with Cockayne syndrome[22] disclosed degeneration of all retinal layers; pigment migration into the photoreceptor layer; thinning of the choriocapillaris; and moderate atrophy of the optic nerve with gliosis. The retinal pigment epithelium was intact with excessive intracellular deposition of lipofuscin. Unusual

pigmented cells were present in the retinal and subretinal space. There was widespread pigment dispersion in the anterior and posterior chambers, and in the trabecular meshwork. The cornea was normal.

Photoreceptor and iris damage in patients with Cockayne syndrome may be caused by ultraviolet light-induced DNA and RNA replication defects. In the absence of effective recovery of DNA and RNA replication, cells that receive large amounts of ultraviolet light degenerate, leading to the clinical ocular features. Additionally, because of the high metabolic activity in photoreceptor and retinal pigment epithelial cells, selective loss of repair of transcriptionally active DNA may result in more damage to these cells as postulated for neurons by Venema and associates.[16]

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Orbital Cellulitis Caused by *Eikenella corrodens*

Ramzi Hemady, M.D., Amy Zimmerman, M.D., Brett W. Katzen, M.D., and James W. Karesh, M.D.

Eikenella corrodens is a gram-negative, facultative anaerobic bacillus with specific culture and growth requirements and unusual antibacterial susceptibilities. It has only recently been recognized as a human pathogen. Ocular and adnexal infections with this organism are rare especially in children. We treated two children with orbital cellulitis caused by _E. corrodens_. One was an 8-year-old boy; the other was an 11-year-old girl. Orbital cellulitis in both patients occurred after an upper respiratory tract infection. Sinusitis and a subperiosteal abscess were present in both patients. _Eikenella corrodens_ and _Streptococcus viridans_ were isolated from the boy; _E. corrodens_ was the sole isolate in the girl. Intravenous ampicillin, prolonged hospitalization, and surgical drainage of the orbit were required to control the infection in both patients. _Eikenella corrodens_ must be considered in the differential diagnosis of orbital cellulitis in children, and ophthalmologists must become familiar with the characteristics of this peculiar organism.

EIKENELLA CORRODENS is a slow-growing facultative, anaerobic, gram-negative bacillus that was first described in 1948 by Henriksen.[1] It was thoroughly characterized in 1958 by Eiken (after whom the organism was named).[2] *Eikenella corrodens* is part of the normal flora of the oral cavity, the nasopharynx, and the upper respiratory, gastrointestinal, and genitourinary tracts.[3,4] The organism usually participates in polymicrobial infections of the head, neck, and viscera.[3-7] Ten cases of ocular and adnexal infections with *E. corrodens* have been published: three with orbital cellulitis,[8,9] two with conjunctivitis,[7] and one each with corneal ulcer,[10] endophthalmitis,[10] dacryocystitis,[7] periorbital cellulitis (unpublished data, Schulman, M. F., Bottone, E. J., Raab, E. L., and Odel, J., "Lid abscess from a human bite," presented as a poster at the American Academy of Ophthalmology meeting, November 1981), and recurrent lacrimal abscess.[11] We treated two children with orbital cellulitis caused by *E. corrodens*.

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From the Department of Ophthalmology (Drs. Hemady, Zimmerman, and Katzen), University of Maryland School of Medicine, Baltimore, Maryland; and the Krieger Eye Institute (Dr. Karesh), Sinai Hospital of Baltimore, Maryland.

Reprint requests to Ramzi Hemady, M.D., University of Maryland Hospital, Department of Ophthalmology, 22 S. Greene St., Baltimore, MD 21201.

Case Reports

Case 1

An 8-year-old boy was seen on Dec. 11, 1989, because of a four-day history of gradually increasing redness of the right eye, eyelid swelling and tenderness, and headache. He had been treated with gentamicin sulfate eyedrops every four hours and amoxicillin, 375 mg every eight hours orally for three days. Ocular history disclosed anisometropic amblyopia of the right eye, successfully treated with patching and spectacles when the boy was 4 years old. Medical history disclosed asthma, sinusitis, and multiple allergies.

On examination, visual acuity in each eye was 20/20. The right eye was 6 mm proptotic, with severely edematous, tense, and tender eyelids. Ocular motility was markedly restricted in all directions of gaze. Pupils reacted normally to light, and ophthalmoscopy showed a normal fundus. The left eye was normal. Temperature was 100.1 F, total white blood cell count was 12,300 cells/mm^3, and erythrocyte sedimentation rate was 117 mm/hr.

The patient was admitted to the hospital where chloramphenicol sodium succinate, 680 mg every six hours, and nafcillin sodium, 750 mg every four hours, were begun intravenously. Gentamicin sulfate eyedrops, every four hours topically, were also begun. Computed tomographic scan of the head and orbits (with contrast) showed a subperiosteal abscess along

the medial wall of the right orbit, and sinusitis of the right maxillary, ethmoid, and sphenoid sinuses. The cerebrospinal fluid was normal. On Dec. 12, 1989, the subperiosteal abscess was surgically drained to release purulent fluid, and an ethmoidectomy and nasal antrostomy were performed via an anterior orbitotomy approach. *Eikenella corrodens* and *Streptococcus viridans* grew from cultures of the drained fluid. Chloramphenicol and nafcillin were subsequently discontinued, and ampicillin, 200 mg/kg of body weight/day intravenously, was begun. Steady improvement followed (confirmed by computed tomography on Dec. 19, 1989). Twelve days postoperatively, however, the right lower eyelid became swollen, and an abscess formed that drained spontaneously; cultures grew *E. corrodens*. Fifteen days after admission, most signs of infection had resolved, ampicillin was discontinued, oral amoxicillin, 250 mg every eight hours was begun, and the patient was discharged from the hospital. Total white blood cell count was 7,600/mm^3 and erythrocyte sedimentation rate was 57 mm/hr. The patient was last seen on April 17, 1990, at which time visual acuity was R.E.: 20/25 and L.E.: 20/20. Extraocular motility was normal and proptosis was absent.

Case 2

An 11-year-old girl was seen on July 23, 1991, because of headache, fever, and periocular swelling of the left side of two days' duration. One week previously, she had suffered from an upper respiratory tract infection. The patient denied history of trauma or sinusitis. Ocular and medical histories were otherwise noncontributory.

On examination, visual acuity was R.E.: 20/20 and L.E.: 20/30. The left eyelids were severely edematous, and diffuse chemosis and conjunctival injection were present (Fig. 1). The globe was 5 mm proptotic and frozen without any extraocular motility. The pupils, posterior segment, and the right eye were normal. Temperature was 101.4 F and white blood cell count was 13,300/mm^3. The patient was admitted to the hospital where clindamycin phosphate, 600 mg every eight hours intravenously, ceftriaxone, 2 g every 12 hours intravenously, and neomycin sulfate-bacitracin zinc-polymyxin B sulfate and erythromycin ophthalmic ointments, every four hours, were begun topically. Computed tomographic scan of the head and orbits (with contrast) disclosed exophthalmos, a subperiosteal abscess of the right medial orbital wall pushing the globe laterally and inferiorly, and right ethmoid and maxillary sinusitis (Fig. 2). On July 23, 1991, the patient underwent a right external ethmoidectomy, inferior meatus nasal antrostomy, and drainage of the subperiosteal abscess. On July 25, 1991, *E. corrodens* grew from cultures of the drained fluid. Clindamycin phosphate was discontinued and ampicillin sodium/sulbactam sodium, 1.5 g every six hours intravenously, was begun. The patient's condition did not improve, however, and repeat computed tomography showed persistence of the subperiosteal abscess (Fig. 3). On July 26, 1991, the patient underwent enlargement of the right external ethmoidectomy and inferior nasal meatus, repeat nasal antrostomy, and repeat incision of left orbital periosteum. She improved rapidly thereafter. By Aug. 1, 1991, she had recovered visual acuity of 20/20 and full ocular motility, and proptosis had resolved (Fig. 4). Topical antibiotics were discontinued. Ampicillin/sulbactam and ceftriaxone were discontinued on Aug. 5, 1991, and amoxicillin/clavulanate potassium, 500 mg every eight hours for 14 days, was begun. The patient was discharged from the hospital on Aug. 6, 1991, at which time she was afebrile and her white blood cell count was 10,600/mm^3. When she was last seen on Sept. 19, 1991, visual acuity in each eye was 20/20, proptosis was absent, and extraocular motility was normal.



Fig. 1 (Hemady and associates). Case 2. Marked periocular edema of the left eye.

Discussion

Eikenella corrodens is part of the normal flora of the oral cavity, nasopharynx, upper respira-

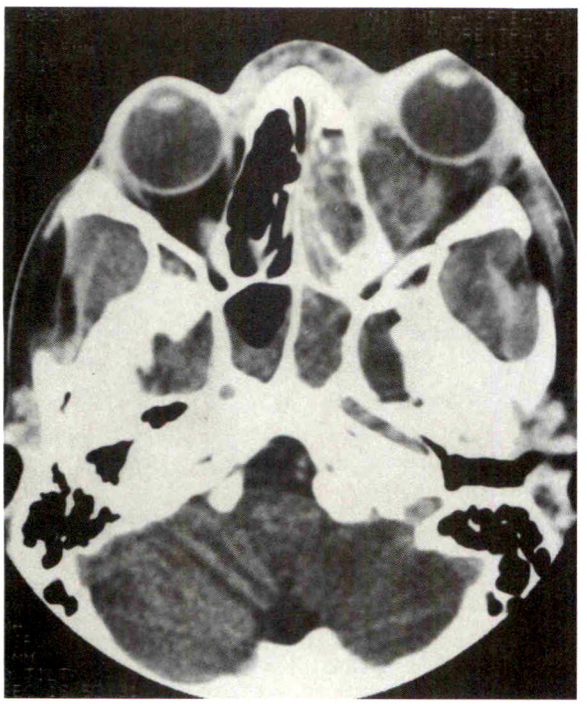


Fig. 2 (Hemady and associates). Case 2. Computed tomography of the orbits (axial plane, with contrast) shows a left subperiosteal abscess of the medial orbital wall and ethmoidal sinusitis.

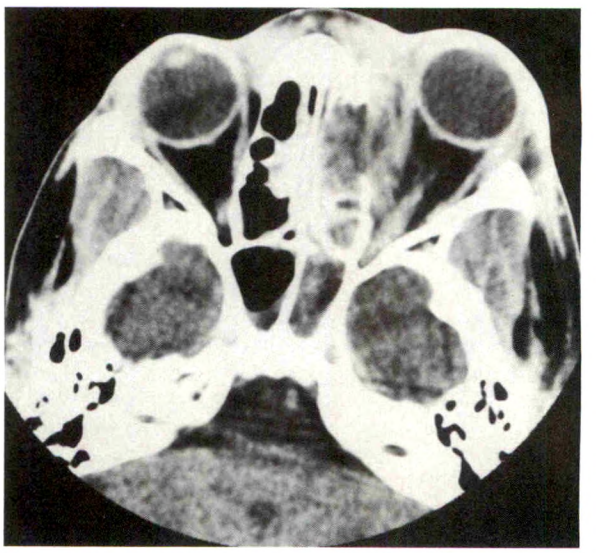


Fig. 3 (Hemady and associates). Case 2. Computed tomography of the orbits (axial plane, with contrast) shows persistence of the subperiosteal abscess of the left orbit after the first orbital drainage procedure.

tory tract, bowel, and urogenital tract,[3,4] but not the conjunctiva,[11] in humans. The organism is a newly recognized human pathogen that has been involved in infections of the central nervous system, head and neck, skin and soft tissue, and respiratory system.[4-7] Sinusitis caused by *E. corrodens* has been associated with central nervous system complications including subdural empyema and cerebral abscess.[12] Infections with *E. corrodens* usually follow contamination through oral secretions or ruptured viscera, more commonly occur in elderly or immunocompromised patients, and are usually part of polymicrobial infections.[4-7]

Eikenella corrodens requires specific laboratory growth conditions: blood or chocolate agar incubated with 5% to 15% CO_2 at 35 to 37 C and 100% humidity anaerobically for a minimum of 72 hours. The colonies are typically small, gray, and pitting with three distinct growth zones. A bleach-like odor is common. Clindamycin (0.5 μg/ml) may be added to the growth medium to facilitate isolation of the organism.[4,7,10]

Eikenella corrodens is commonly resistant to many broad-spectrum antibiotics such as the aminoglycosides and penicillinase-resistant penicillins, and to clindamycin and metronidazole. The organism is usually susceptible to penicillin, ampicillin, vancomycin, erythromycin, and chloramphenicol.[4-7,10] An agar diffusion method of antimicrobial susceptibility with a standardized inoculum is recommended.[4,10] Both *E. corrodens* isolates cultured from the patients described herein were susceptible to

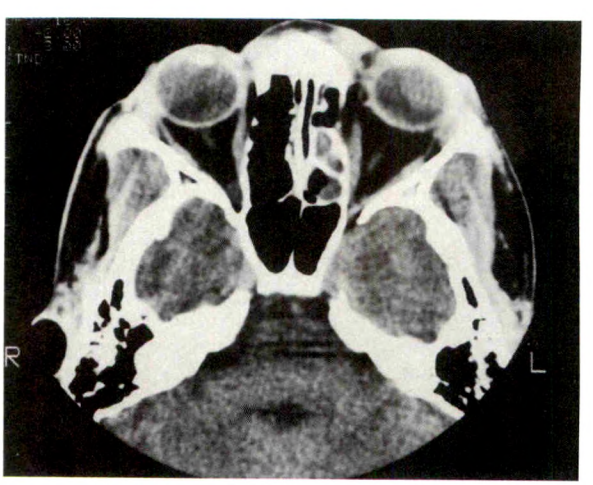


Fig. 4 (Hemady and associates). Case 2. Computed tomography of the orbits (axial plane, with contrast) shows resolution of the left orbital abscess and left ethmoidal sinusitis.

ampicillin, chloramphenicol, tetracycline, and cefamandole.

Ocular and adnexal infections with *E. corrodens* are rare. This may not, however, reflect the true incidence of ocular infections with the organism as specific growth requirements, slow growth in culture, and polymicrobial infections make isolation of *E. corrodens* difficult.

In 1979, Schwartz and colleagues[8] were the first to report ocular infections with *E. corrodens*. In one patient, orbital cellulitis was polymicrobial. The infection was successfully treated with intravenous penicillin but required surgical drainage. The patient also had sinusitis. In the second patient, orbital cellulitis caused by *E. corrodens* was the result of an infected prosthesis after orbital exenteration. In 1981 a case of periorbital cellulitis caused by *E. corrodens* complicating a human bite was described (unpublished data, Schulman, M. F., Bottone, E. J., Raab, E. L., and Odel, J., "Lid abscess from a human bite," presented as a poster at the American Academy of Ophthalmology meeting, November 1981). In 1983, Harris[9] described a patient with a subperiosteal abscess caused by a polymicrobial infection including *E. corrodens*. The patient lost light perception despite treatment with penicillin and nafcillin intravenously and orbital drainage. The patient also had sinusitis. In a report of 33 cases of infection with *E. corrodens* in a general hospital, Stoloff and Gillies[7] identified three cases of ocular infections. One patient developed a polymicrobial dacryocystitis in an eye with a prosthesis. Two patients developed conjunctivitis; one was unilateral and polymicrobial, the other bilateral in which *E. corrodens* was the only isolate. Dua and associates[11] described a patient with a recurrent lacrimal abscess secondary to trauma from which *E. corrodens* and *Haemophilus influenzae* were isolated. Klein, Couch, and Thompson[10] described two patients with ocular infections caused by *E. corrodens*. One developed a corneal ulcer secondary to trauma that responded to fortified topical tobramycin; *E. corrodens* was the sole isolate. The second patient developed endophthalmitis two days after repair of a penetrating corneal injury. Vitreous cultures grew *E. corrodens* among other organisms. Treatment consisted of vitrectomy, intravitreous, intravenous, and fortified topical cefazolin and gentamicin, and oral prednisone.

Eikenella corrodens was the only organism isolated from Case 2 in our study; this was the third reported case in which *E. corrodens* was the sole isolate in an ocular infection.[7,10] These data confirm that *E. corrodens* may be an ocular pathogen, alone or as part of polymicrobial infections, in young, immunocompetent individuals.

Ocular infections with *E. corrodens* usually follow trauma or sinusitis.[7,8,10,11] In our patients sinusitis may have eroded into the orbit, leading to the development of a subperiosteal abscess and orbital cellulitis. A subperiosteal abscess is an advanced stage of orbital cellulitis requiring prompt treatment as visual loss and extension into the central nervous system may follow.[12,13] Because ocular and adnexal infections with *E. corrodens* tend to be rapidly progressive, treatment should be aggressive; intravenous antibiotics, surgical drainage, and prolonged hospitalization were required in both of our patients.

Eikenella corrodens may cause ocular and adnexal infections, alone or as part of polymicrobial infections, in healthy individuals of all ages. The organism must be suspected in cases of orbital cellulitis especially in the presence of sinusitis and evidence of a subperiosteal abscess. Efforts should be made to culture *E. corrodens* from patients with orbital cellulitis as the actual rate of infection with this organism may be higher than that deduced from the current literature. We suggest the use of an antibiotic effective against *E. corrodens*, such as ampicillin, in the initial management of orbital cellulitis.

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OPHTHALMIC MINIATURE

Now, on very dark nights, light is a deadly enemy to piloting; you are aware that if you stand in a lighted room, on such a night, you cannot see things in the street to any purpose; but if you put out the lights and stand in the gloom you can make out objects in the street pretty well. So, on very dark nights, pilots do not smoke; they allow no fire in the pilot-house stove, if there is a crack which can allow the least ray to escape; they order the furnaces to be curtained with huge tarpaulins and the skylights to be closely blinded. Then no light whatever issues from the boat.

Mark Twain, *Life on the Mississippi*
New York, Bantam Books, 1988, p. 57

Diode Laser Photocoagulation for Prethreshold, Posterior Retinopathy of Prematurity

Thomas N. Fleming, M.D., Paul E. Runge, M.D., and Steven T. Charles, M.D.

Nine infants with posterior retinopathy of prematurity were treated by using the diode laser through an indirect ophthalmoscopic delivery system. Treatment was commenced as soon as plus disease (defined as tortuosity and dilation of posterior vessels) developed. We defined posterior retinopathy of prematurity as retinopathy of prematurity located in zone 1 (the limits of zone 1 are defined as twice the disk-fovea distance in all directions from the optic disk, that is, an arc of 60 degrees centered on the optic disk) or the posterior one half of zone 2 (zone 2 extends from the edge of zone 1 peripherally to a point tangential to the nasal ora serrata and around to an area near the temporal anatomic equator). Disease regressed in all eyes. These results are encouraging and represent an improvement over the results obtained by allowing these eyes to reach threshold (threshold disease is defined as 5 or more contiguous or 8 total clock hours of neovascularization in zone 1 or 2 in the presence of plus disease) before intervention.

THE MULTICENTER TRIAL of cryotherapy for retinopathy of prematurity demonstrated that cryotherapy could decrease the number of unfavorable outcomes (defined as retinal detachment or fold of the posterior pole involving the macula) in patients with threshold retinopathy of prematurity.[1] In that study, 75% of zone 1 eyes and 22% of zone 2 eyes treated at threshold had unfavorable outcomes. Landers and associates[2] described the application of argon laser to treat the entire avascular retina in a manner similar to that used in the cryotherapy study. A subsequent study at the Wills Eye Hospital[3] compared the use of the indirect argon laser to cryotherapy in stage 3 threshold (defined as a minimum of 5 contiguous or 8 total clock hours of neovascularization in zone 1 or zone 2 in the presence of plus disease) retinopathy of prematurity. They found that the laser was as effective as cryotherapy in reducing the number of unfavorable outcomes in this condition.

Because the course of this disease is dramatically different depending on the zone or zones involved, and the circumferential extent and the presence or absence of plus disease, the definitions should be clearly understood. Zone 1 (posterior pole or inner zone) consists of a circle centered on the optic disk, the radius of which is twice the disk-fovea distance. Zone 2 extends from the edge of zone 1. Its outer limits are defined by a circle, the radius of which is the distance from the optic nerve to the nasal ora serrata. The temporal limit of this zone is near the anatomic equator. Plus disease is defined as progressive vascular incompetence as noted by increasing dilation and tortuosity of the peripheral retinal vessels, iris vasculature engorgement, pupillary rigidity, and vitreous haze. When these vascular changes are so marked that the posterior veins are enlarged and the arteries are tortuous, plus disease is present. Stage 3 retinopathy of prematurity is defined as the presence of a ridge with extraretinal fibrovascular proliferation. Threshold disease is defined as five or more contiguous or eight cumulative clock hours of stage 3 retinopathy of prematurity in zone 1 or 2 in the presence of plus disease.[4]

In general, retinopathy of prematurity has been assumed to progress predictably through its various stages. However, neovascularization in zone 1 or posterior zone 2 does not follow the usual progression for this condition. The characteristic fashion in which retinopathy of prematurity progresses from stage 1 to stage 3 (stage 1 is characterized by the presence of a demarcation line between vascularized and

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From the Center for Retina Vitreous Surgery, and the Department of Ophthalmology, University of Tennessee, Memphis, Tennessee.

Reprint requests to Steven T. Charles, M.D., Center for Retina Vitreous Surgery, 6401 Poplar Ave., Suite 190, Memphis, TN 38119.

nonvascularized retina; stage 2 is characterized by the presence of a demarcation line that has height, width, and volume, which is called a ridge), which culminates in an easily identifiable ridge with neovascularization, does not occur in this more aggressive posterior variety of retinopathy of prematurity. Instead, the vessels may end in a flat neovascular syncytial network that can be difficult to visualize and is therefore easily missed.[5] By the time this network becomes obvious, it may extend for many clock hours, having developed what appear to be arteriovenous shunts of the distal ends of the major retinal vessels. Subsequently, these shunts join and in so doing, a 360-degree vascular ridge develops, which rapidly progresses to retinal detachment. In our opinion, waiting for threshold retinopathy of prematurity to develop in these eyes with posterior disease before intervening results in an unacceptably high failure rate. Recently, two groups supported our opinion.[6,7]

To improve the outcome for these infants with posterior disease, we used the indirect diode laser to treat all eyes with zone 1 or posterior zone 2 retinopathy of prematurity as soon as plus disease was noted. Many of these eyes had disease at the border of zones 1 and 2, and in that circumstance were classified as zone 1. Eyes that had disease in posterior zone 2 had vessels that crossed the border of zones 1 and 2, but clearly did not extend into the anterior portion of zone 2. There was no difficulty in determining that the vessels in these eyes were in the posterior rather than the anterior half of zone 2.

Material and Methods

Patients were enrolled between Nov. 1, 1991, and Jan. 6, 1992. All patients weighed less than 1,210 g. Each patient was examined at four to six weeks post partum and at one-week intervals thereafter. Patients were treated at or within three days of developing plus disease. No eye had neovascularization at the time of treatment. Informed consent was obtained from the mother of each patient.

A diode laser (OcuLight SLX, LIO 500, Iris Medical Instruments, Inc., Mountain View, California) with an indirect ophthalmoscopic delivery system was used. The wavelength of the laser is 810 nm. The average energy required was 180 to 200 mW with a duration of 300 msec. The continuous mode of this laser system was most often used. The energy was delivered through a +28-diopter Nikon lens, which resulted in a retinal spot size of 676 μm. This assumes that the refractive state of the premature infants' eyes is emmetropia, which on average is correct.[8]

We found it unnecessary to use any sedation or anesthesia other than two drops of topical 0.1% tetracaine for this procedure. Many infants develop apnea and bradycardia if given intravenous sedation/analgesia. This had been our protocol when performing cryopexy on these infants, a procedure which we judge to be more traumatic than the laser treatment. Several of our neonatologists have been reluctant to allow us to use any intravenous sedation/analgesia in the more unstable infants. Many of the infants who require treatment fall within this category.

An Alfonso eyelid speculum was used with the aid of scleral depression as required. Laser burns were applied to the avascular retina for 360 degrees, all the way to the ora serrata. The mesenchymal ridge was avoided. Spots were placed one-half burn width apart by using a dull gray-white laser photocoagulation mark as the endpoint. We specifically made an effort to avoid producing brilliant white photocoagulation lesions, which represent overtreatment. Defocusing the laser increases the spot size and decreases the energy density, which is a useful technique in adjusting the retinal burn intensity. Both eyes of each patient were treated in the same session. If a second session of treatment was necessary, it was performed within 17 days of the initial treatment. The indication for re-treatment was the presence of untreated skip areas with plus disease persisting at the two-week follow-up examination. Re-treatment was applied only to the skip areas and only one patient required re-treatment.

Results

Nine infants were treated in this study. All 18 eyes have shown complete regression of the plus disease; that is, vessel caliber decreased to normal size, the vessels narrowed as they coursed distally and lost their abnormal tortuosity, and retinal development progressed in its

normal plane. Disease regressed in 17 of 18 eyes (94%) and no neovascularization developed. However, one patient (Patient 7) had four clock hours of contiguous neovascularization temporally in the right eye three to four weeks after laser treatment. No skip areas were present in this eye and the plus disease and neovascularization regressed by the fifth-week follow-up examination without further intervention. All eyes have been followed up for a minimum of 24 weeks after treatment and no eye had an unfavorable outcome (no retinal detachments, and no retinal dragging or folds).

All patients were treated by using only topical anesthesia. The procedure was well tolerated and additional sedation/analgesia was judged to be unnecessary by the neonatology staff. No untoward systemic effects were noted except for brief episodes of bradycardia that abated with temporary removal of the eyelid speculum and tactile stimulation in two patients. No retinal, preretinal, or vitreous hemorrhages resulted from treatment. One patient (Patient 2) was re-treated 17 days after the first treatment because of the persistence of plus disease in the presence of limited skip areas.

The birth weights of the infants treated ranged from 580 to 1,200 g, with a mean of 815 g. The mean gestational age at birth was 26 weeks. The average age at treatment was 33 to 34 weeks gestational age (seven to eight weeks post partum). The average number of laser burns used was 960 (Table).

Discussion

We believe that this protocol represents an improvement over the results that were obtained by treating with laser or cryopexy once threshold disease was present. Eyes with posterior plus disease are at high risk of attaining threshold, and treating at that stage with cryotherapy results in a 75% chance of an unfavorable outcome (for zone 1 disease). The chance of an unfavorable outcome for posterior zone 2 disease would be expected to range between 22% and 75%, although the results for anterior and posterior zone 2 disease have not been definitively compared. We see little reason to wait beyond the development of plus disease

TABLE
DIODE LASER TREATMENT OF PRETHRESHOLD, POSTERIOR RETINOPATHY OF PREMATURITY

PATIENT NO., AGE (WKS),* GENDER	RACE†	BIRTH WEIGHT (G)	EYE	NO. OF LASER BURNS	RETINAL ZONE AFFECTED	GESTATIONAL AGE (WKS) AT TREATMENT
1, 28, F	W	1,200	R.E.	738	Posterior II	35
			L.E.	760	Posterior II	35
2, 24, F	B	580	R.E.	850	Posterior II	32
			L.E.	950	Posterior II	32
3, 25, M	B	923	R.E.	1,146	Anterior I	32
			L.E.	1,241	Anterior I	32
4, 28, M	B	670	R.E.	1,139	Posterior II	38
			L.E.	777	Posterior II	38
5, 24, F	B	585	R.E.	1,298	Anterior I	31
			L.E.	1,063	Anterior I	31
6, 28, M	W	950	R.E.	1,010	Anterior I	35
			L.E.	1,038	Anterior I	35
7, 26, M	B	860	R.E.	838	Anterior I	33
			L.E.	844	Anterior I	33
8, 28, M	B	908	R.E.	1,000	Anterior I	35
			L.E.	950	Anterior I	35
9, 24, M	B	665	R.E.	809	Posterior II	32
			L.E.	825	Posterior II	32

*Estimated gestational age at birth.
†W indicates white and B indicates black.

before commencing treatment of posterior retinopathy of prematurity. The right eye of Patient 7 in our study developed neovascularization even after complete treatment with the diode laser. We believe this development demonstrates the aggressive course of posterior retinopathy of prematurity and clearly distinguishes it from its more benign anterior counterpart.

It has recently been suggested that we lower the threshold criteria for the treatment of posterior retinopathy of prematurity, and consider it a separate entity from its more anterior counterpart, because of the extremely poor prognosis of this condition (95% unfavorable outcome without treatment and 75% unfavorable outcome with treatment).[6] Because of the high risk of poor outcome in these eyes, we believe that earlier treatment is justified. Additionally, we believe the course of posterior zone 2 disease differs considerably from that of anterior zone 2 disease in that the progression of posterior zone 2 disease is similar to that of zone 1 disease and therefore should receive earlier intervention. The key appears to be intervening as soon as plus disease develops.

This study shows that excellent results can be obtained by treating posterior retinopathy of prematurity with the diode laser as soon as plus disease develops. We believe that a study in which patients are randomly assigned to treatment and that compares this protocol to treating at threshold may be warranted.

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Posterior Segment Changes in Membranoproliferative Glomerulonephritis

David D. Kim, M.D., William F. Mieler, M.D., and Mitchell D. Wolf, M.D.

Membranoproliferative glomerulonephritis is a renal disorder characterized by proliferation of cells and changes in the basement membrane of the glomerulus. The disease is divided into three subtypes: type I, characterized by the presence of subendothelial electrondense deposits; type II, characterized by deposition of electrondense material of unknown origin in the lamina densa of the glomerular basement membrane; and type III, characterized by lesions having both type I and type II qualities. Specific posterior segment changes have been reported with membranoproliferative glomerulonephritis type II. We examined three patients with membranoproliferative glomerulonephritis type II and two patients with type III disease. All three patients with type II disease had Bruch's membrane and retinal pigment epithelial changes, whereas both patients with type III disease had normal posterior segments.

MEMBRANOPROLIFERATIVE glomerulonephritis encompasses a group of renal disorders marked by proliferation of mesangial cells and thickening of the glomerular basement membrane. The disease is divided into three types according to its microscopic structure. Type I disease is characterized by the presence of subendothelial electrondense deposits with capillary wall thickening and narrowing of the capillary lumen. By immunofluorescence, C3, IgG, C1q, and C4 are deposited in the subendothelial basement membrane. These features suggest that membranoproliferative glomerulonephritis type I is a chronic immune complex glomerulonephritis, although the exact origin remains unclear.[1]

In type II disease, electron microscopy studies show extensive replacement of the lamina densa by a uniform, dark-staining material within the mesangium, Bowman's capsule, and tubular basement membrane. Type II disease does not appear to be an immune deposit disease. Although C3 is present in small amounts within the basement membrane, the actual electrondense deposits that characterize the disease are devoid of C3, IgG, C1q, and C4. The exact nature of these electron deposits has yet to be discovered.[1]

Clinically, there are only minor differences between the two types. In general, both types are found in children 5 years and older or in young adults less than 30 years of age. Membranoproliferative glomerulonephritis comprises approximately 10% of the idiopathic nephrotic syndrome.[2] Type I disease occurs twice as frequently as type II. Additionally, type I disease appears to progress more slowly than type II disease, reaching end stage in 15 to 20 years, whereas type II reaches end stage in six to ten years.[2] Furthermore, type II tends to be an unremitting disease, often recurring even after renal transplant.

A rare variant, membranoproliferative glomerulonephritis type III, has also been described.[3] This entity has both subendothelial and subepithelial deposits, characteristics of type I and type II disease.

Ocular posterior segment changes in membranoproliferative glomerulonephritis type II were first reported in 1989 by Duvall-Young, MacDonald, and McKechnie.[3] In their study, they demonstrated drusenlike deposits in Bruch's membrane and choriocapillaris in patients with type II disease. Subsequent histopathologic studies showed that the deposits were not drusen but were morphologically similar to deposits found within the glomerular basement membrane of patients with membranoproliferative glomerulonephritis type II dis-

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From the Department of Ophthalmology, Medical College of Wisconsin, Milwaukee, Wisconsin. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York, New York, and by Core Grant EY01931 from the National Eye Institute.

Reprint requests to William F. Mieler, M.D., 8700 W. Wisconsin Ave., Milwaukee, WI 53226.

ease.[3,4] In a subsequent study by Leys and associates,[5] subretinal neovascularization was reported in patients with type II disease.

The aim of this study was to confirm and characterize the ocular posterior segment lesions in patients with renal biopsy-proven membranoproliferative glomerulonephritis type II disease. Additionally, the posterior segments of patients with membranoproliferative glomerulonephritis type III disease were assessed to determine if they had similar lesions as seen in patients with type II disease.

Subjects and Methods

The five patients in this study all underwent renal biopsy and were examined in the nephrology department at the Medical College of Wisconsin or the Zablocki Veterans Administration Hospital in Milwaukee. Membranoproliferative glomerulonephritis type II disease was diagnosed in two women and one man. Membranoproliferative glomerulonephritis type III disease was diagnosed in the other two patients, both men. All patients underwent a complete ophthalmic examination, fundus photography, and fluorescein angiography. The characteristics of the five patients are summarized in the Table.

Results

The three patients with membranoproliferative glomerulonephritis type II were noted to have posterior segment changes (Table). In Case 1, diffuse, small drusenlike deposits were observed in the posterior pole and throughout the periphery (Fig. 1), whereas in Case 2 larger aggregated deposits were seen (Fig. 2). The peripheral subretinal deposits and accompanying retinal pigment epithelial alteration gave the fundus a salt-and-pepper appearance, most notably in Case 1. In Case 3, no deposits or peripheral salt-and-pepper changes were evident clinically. Angiographically, however, diffuse areas of discrete transmission defects were noted in the periphery (Fig. 3). In Cases 1 and 2, fluorescein angiography allowed the deposits to be more easily visualized (Fig. 1, middle left and right and bottom left; Fig. 2, bottom left and right). Additionally, late phases of the angiogram from Case 1 documented mild disk staining, most likely secondary to hypertension and not directly related to the membranoproliferative glomerulonephritis.

We found no correlation between the length of disease and the presence of the deposits, though our study consisted of only three patients. Although membranoproliferative glomerulonephritis type II had been diagnosed in

TABLE
CHARACTERISTICS OF PATIENTS

CASE NO., AGE (YRS), GENDER	DIAGNOSIS	AGE AT ONSET (YRS)	DISEASE DURATION (YRS)	DISEASE STATUS	FUNDUS CHANGES
1, 19, F	Membranoproliferative glomerulonephritis II	9	10	Posttransplant × 3; normal renal function*	Basal lamina deposits; retinal pigment epithelial atrophy
2, 30, F	Membranoproliferative glomerulonephritis II	24	6	Postrenal transplant; normal renal function	Basal lamina deposits; retinal pigment epithelial atrophy
3, 30, M	Membranoproliferative glomerulonephritis II	18	22	Postrenal transplant; normal renal function	Clinically normal fundus; fluorescein angiography with evidence of diffuse retinal pigment epithelial atrophy
4, 70, M	Membranoproliferative glomerulonephritis III	50	10	Remission with no medication; normal renal function	Normal fundus
5, 61, M	Membranoproliferative glomerulonephritis III	51	10	Chronic furosemide therapy, no corticosteroids for 9 yrs; chronic renal insufficiency (blood urea nitrogen ≈ 28 mg/dl; creatinine ≈ 1.9 mg/dl)	Normal fundus

*Normal renal function: blood urea nitrogen < 20 mg/dl, creatinine < 1.0 mg/dl.

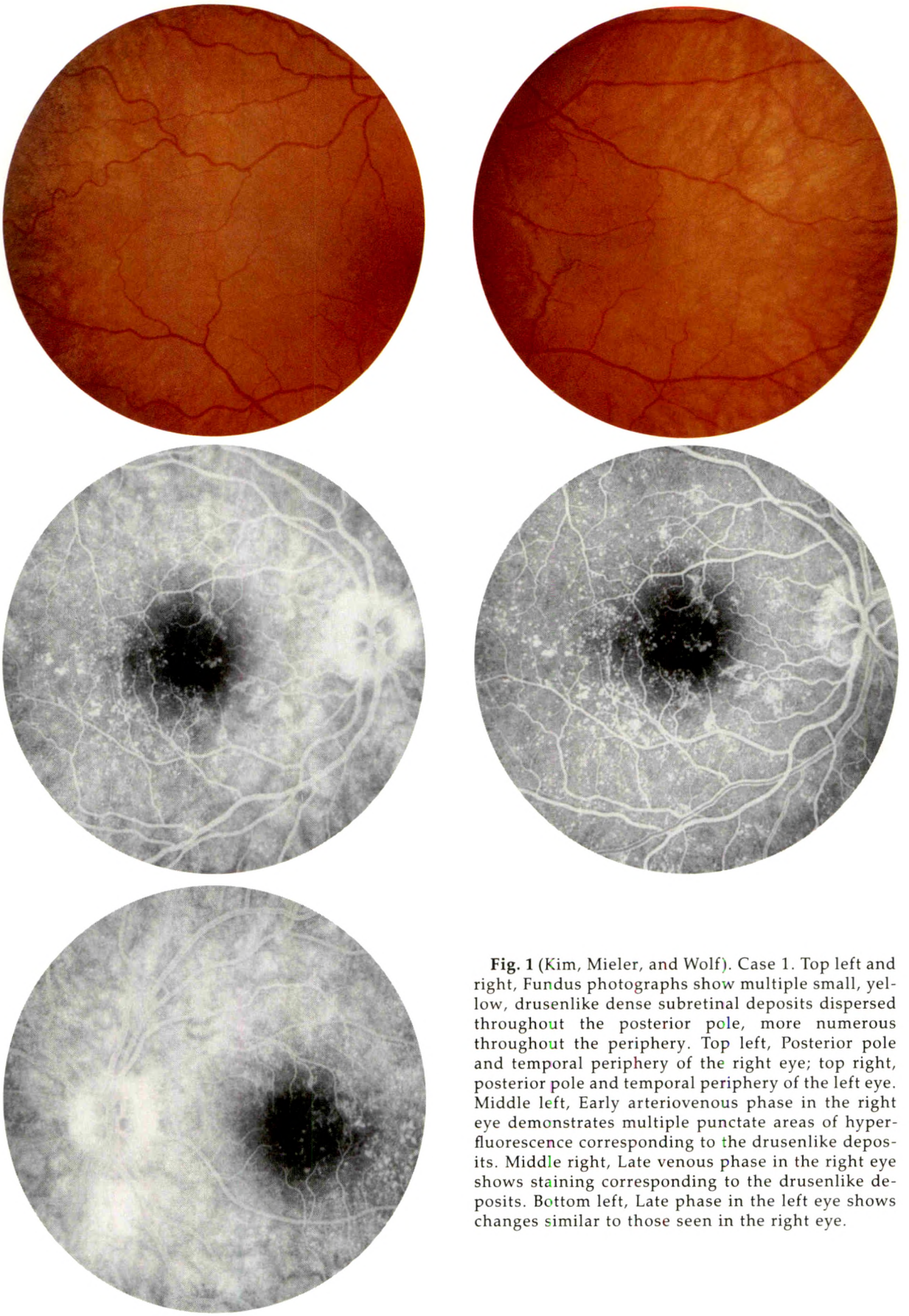


Fig. 1 (Kim, Mieler, and Wolf). Case 1. Top left and right, Fundus photographs show multiple small, yellow, drusenlike dense subretinal deposits dispersed throughout the posterior pole, more numerous throughout the periphery. Top left, Posterior pole and temporal periphery of the right eye; top right, posterior pole and temporal periphery of the left eye. Middle left, Early arteriovenous phase in the right eye demonstrates multiple punctate areas of hyperfluorescence corresponding to the drusenlike deposits. Middle right, Late venous phase in the right eye shows staining corresponding to the drusenlike deposits. Bottom left, Late phase in the left eye shows changes similar to those seen in the right eye.

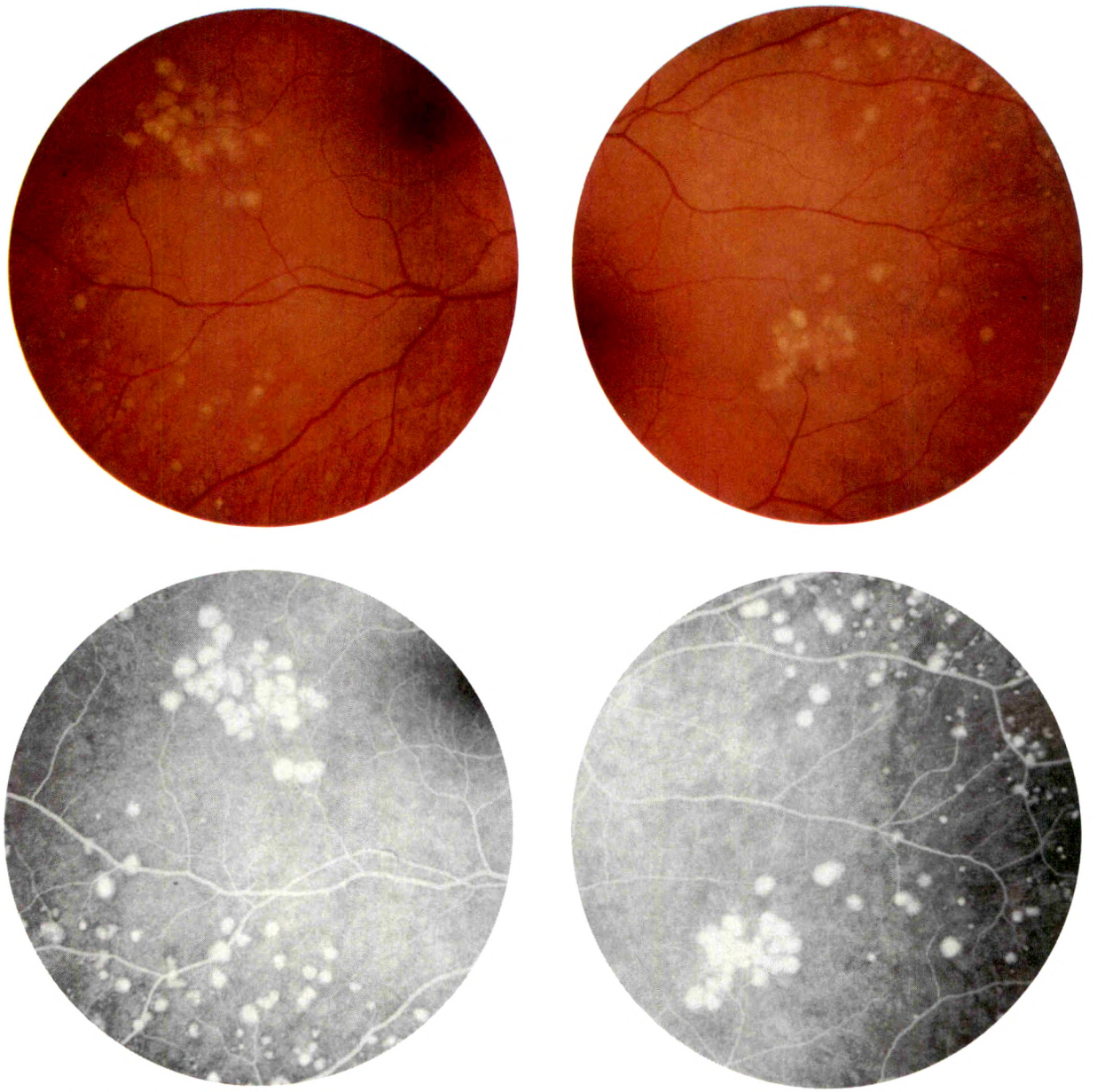


Fig. 2 (Kim, Mieler, and Wolf). Case 2. Top left and right, Fundus photographs show multiple larger, yellow drusenlike dense subretinal deposits located primarily temporal to the macula, as well as scattered throughout the periphery. Top left, Posterior pole and temporal periphery of the right eye; top right, posterior pole and temporal periphery of the left eye. Bottom left, Midvenous phase of the right eye posterior pole and inferotemporal periphery demonstrates multiple punctate areas of hyperfluorescence corresponding to the drusenlike deposits in the top photographs. Bottom right, Late venous phase in the left eye posterior pole and temporal periphery shows changes similar to those in the right eye.

Case 3 for 22 years, the patient showed only minimal changes that only were detected angiographically. In contrast, the patient with the most striking deposits (Case 2) had the diagnosis for only six years.

The three patients with membranoproliferative glomerulonephritis type II had visual acuity of 20/20 with normal visual fields. None of the patients had subretinal neovascularization clinically or angiographically. All three patients had renal transplants and were taking similar immunosuppressive medications in-

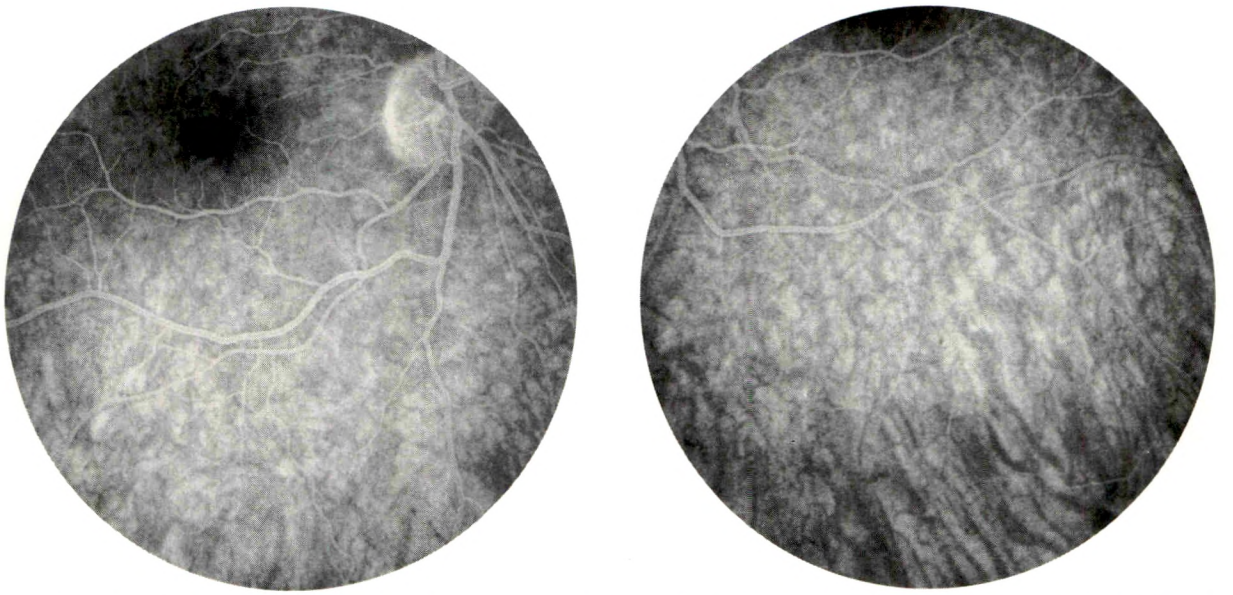


Fig. 3 (Kim, Mieler, and Wolf). Case 3. Left, Late venous phase of the right eye posterior pole and inferior periphery shows subtle areas of transmission defects throughout the periphery; right, late venous phase of the left eye posterior pole and inferior periphery shows minimal focal areas of transmission defect. There is an absence of punctate areas of hyperfluorescence as seen in Figures 1 and 2.

cluding cyclosporine, azathioprine, and corticosteroids. In the two patients with type III disease, no evidence of drusenlike deposits was found clinically or angiographically (Fig. 3). Both of the patients had visual acuity of 20/20 and normal visual fields. Of note, neither of the patients with membranoproliferative glomerulonephritis type III had renal transplants and their disease was in remission. Neither of the patients had taken corticosteroids for nine years.

Discussion

Membranoproliferative glomerulonephritis type I is characterized by subendothelial deposits, whereas type II disease is characterized by subepithelial deposits of glomerular basement membrane. If the same histopathologic changes occur in both the renal and ocular systems of patients with type II disease, it follows that subepithelial deposits within Bruch's membrane in type II disease should be visible clinically. The histopathologic study of the deposits found in the fundus of a patient with type II disease, performed by Duvall-Young, MacDonald, and McKechnie,[3] confirmed the presence of dense deposits within the inner collagenous layer of Bruch's membrane, which were biochemically similar to the deposits found in the glomerular basement membrane of the same patient.

In our study, we clearly showed dense deposits within the posterior segments in Cases 1 and 2 of patients with membranoproliferative glomerulonephritis type II. Additionally, we showed diffuse retinal pigment epithelial alteration in Case 3. Exactly what those deposits are and why there is such a range of clinical expression have not been determined. Because IgG, C3, C1q, and C4 have not been identified in those deposits, one can assume that an autoimmune response cannot account for the deposits.[1]

Posterior segment findings in membranoproliferative glomerulonephritis type II appear to be common. Of 24 patients with type II disease, 22 (92%) were found to have clinical and angiographic changes.[6] The two patients without clinical evidence had renal disease of only two and 13 months' duration, respectively. All patients with renal disease 16 months or longer had posterior segment abnormalities. The earliest features consist of small subretinal nodules similar to basal laminar drusen. These lesions initially may be isolated or may be grouped in clusters.[6,7] Initially these nodules may be difficult to visualize ophthalmoscopically, though they are easily visualized angiographically. The

development of dense deposits does not relate to previous renal transplant or immunosuppressive therapy.[6]

As the renal and retinal disease process progresses, the number of subretinal nodules increases. Additionally, the nature of the nodules changes and larger subretinal nodules appear to be similar to age-related exudative or soft drusen. When renal disease has persisted for more than 17 years, atrophic changes in the retina and pigment epithelium are observed. Additionally, pigment epithelial detachment and subretinal neovascularization may occur in patients with a history of renal disease of more than 15 years.[8]

Leys and co-workers[5] reported subretinal neovascularization in three patients with type II disease for between 12 and 22 years. Each of the patients had extensive drusen or pigment epithelial alterations throughout the fundus. Untreated subfoveal membranes resulted in severe central visual loss, whereas photocoagulation was successful in the preservation of vision in an additional patient. It is, therefore, important to instruct and monitor patients for signs and symptoms of subretinal neovascularization to prevent possible loss of vision. Our study and the previous reports suggest that visual loss does not occur secondary to the development of dense-deposit disease alone.

In addition to the study of membranoproliferative glomerulonephritis type II, we examined two patients with membranoproliferative glomerulonephritis type III. Although renal biopsy disclosed both subendothelial and subepithelial deposits, no ocular posterior segment abnormalities were noted, clinically or angiographically. Because of the small sample size, we cannot make any broad conclusion. The finding of a normal posterior segment in type III disease suggests that it may more resemble type I disease. Ocular examination of patients with type I disease showed normal posterior segments, both clinically and angiographically.[9] Histopathologic study will eventually clarify these findings in more detail.

Despite the subretinal nodules having the clinical appearance of drusen, the histopathologic results are identical to the deposits in the glomerulus. These deposits of electrondense material are found within the glomerular basement membrane. Both Bruch's membrane and the glomerular membrane are structurally similar in that both are selectively and directionally permeable with similar positively charged and high heparin-sulfated content. The morphologic similarities between the glomerulus and the choriocapillaris-Bruch's membrane complex may underlie the common dense deposits acquired in membranoproliferative glomerulonephritis type II.

Although the inner collagenous zone of Bruch's membrane is thicker than the glomerular basement membrane, the glomerular basement membrane also undergoes focal thickening with age. This is similar in appearance to the aging changes of Bruch's membrane.[3] Breaks in the glomerular basement membrane similar to angioid streaks in Bruch's membrane have also been described.[10]

Although membranoproliferative glomerulonephritis type II is a rare entity, most patients will exhibit posterior segment abnormalities including dense deposits resembling drusen, a salt-and-pepper retinopathy, and possible subsequent development of subretinal neovascularization. Patients should have an ophthalmic examination on a regular basis and be monitored for changes in central visual function.

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OPHTHALMIC MINIATURE

In the matter of eyes, also, my acquaintance was pre-eminently endowed. Either one of such a pair was worth a couple of the ordinary ocular organs. They were a deep hazel exceedingly large and lustrous; and there was perceptible about them, ever and anon, just that amount of interesting obliquity which gives pregnancy to expression.

Edgar Allen Poe, "The Man That Was Used Up," *The Fall of the House of Usher and Other Stories*
New York, Penguin Books, 1980, p. 191

Posterior Capsulotomy as a Complication of Indirect Laser Photocoagulation

Vinod Lakhanpal, M.D., Deeba Husain, M.D., and Stanley S. Schocket, M.D.

Two pseudophakic patients with posterior chamber intraocular lens implants and intact posterior capsules underwent indirect laser photocoagulation during their immediate postoperative period (24 and 72 hours postoperatively, respectively). Laser treatment was indicated for a retinal break noted after vitrectomy and scleral buckling in one patient and after peribulbar perforation during cataract extraction in the other patient. Ocular media were hazy because of vitreous haze and hemorrhage in both eyes and higher power laser settings were required to produce adequate chorioretinal burns during photocoagulation. Inadvertent large posterior capsulotomy as a complication was noted in both eyes. High-power settings and hazy ocular media are risk factors toward this complication. We recommend that slit-lamp examination be performed before, during, and after indirect laser treatment, especially when higher power settings are required.

THE BINOCULAR INDIRECT LASER delivery system is a versatile mode of retinal laser photocoagulation. This system is especially useful when laser treatment cannot be applied through a slit-lamp delivery system. Its primary advantage is the wide field of view afforded by indirect ophthalmoscopy, so that the peripheral retinal lesions can be visualized with scleral depression and can be treated.[1] It allows retinal laser treatment without the application of a contact lens, thus avoiding any pressure applied to the eye, which may be detrimental in the immediate postoperative period, such as after cataract extraction. The system is also useful to treat patients with focal lens opacities, small pupils, and patients who cannot cooperate with the slit-lamp delivery system.[2]

Various complications described during indirect laser photocoagulation include corneal and iris burns,[3,4] choroidal hemorrhage, and macular burns.[5] Recently, a melted haptic in a pseudophakic patient with a retinal detachment and creation of transient anterior subcapsular cataracts during photoablation in a patient with retinopathy of prematurity during indirect laser treatment have been described.[6,7] We managed two cases of accidental posterior capsulotomy during indirect laser photocoagulation treatment for retinal breaks during their immediate postoperative period.

Case Reports

Case 1

A 39-year-old man had undergone an extracapsular cataract extraction with posterior chamber intraocular lens implantation in the left eye 72 hours before referral. A small vitreous hemorrhage, possibly secondary to inadvertent ocular perforation during periocular injection, was suspected and the patient was referred to us for further treatment. On examination, the best-corrected visual acuity in the left eye was 20/60. Slit-lamp examination showed well-placed posterior chamber intraocular lens implantation with an intact posterior capsule and mild flare with trace cells. Indirect ophthalmoscopy disclosed an inferior vitreous hemorrhage that surrounded a linear white bare sclera with a horseshoe retinal break in the infratemporal quadrant. The retina, however, was flat. The retinal tear was treated with krypton laser by using an indirect laser photocoagulation delivery system with the patient under retrobulbar lidocaine hydrochloride block. Two hundred laser spots of 200-μm spot size were applied at 300-mW power at 0.5 second. At six weeks of follow-up, visual acuity in the left eye

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From the Retina Service, Department of Ophthalmology, University of Maryland, Baltimore, Maryland.

Reprint request to Vinod Lakhanpal, M.D., Retina Service, University of Maryland Hospital, Room N6W46, 22 S. Greene St., Baltimore, MD 21201.

was 20/20. Slit-lamp examination at this time disclosed an inadvertent large 6-mm posterior capsulotomy with smooth margins and a stable posterior chamber intraocular lens. Ophthalmoscopy showed a flat retina with good chorioretinal pigmentation around the area of the scleral perforation and retinal tear, with total absorption of the vitreous hemorrhage.

Case 2

A 54-year-old man underwent pars plana vitrectomy, scleral buckling, endolaser photocoagulation, and air-fluid exchange for a macula-off rhegmatogenous retinal detachment of the left eye with a large superotemporal horseshoe break. First-day postoperative examination disclosed slightly hazy media with 50% air bubble. The retina was flat with the tear well placed on the buckle. However, only half of the retinal tear was noted to have been treated intraoperatively with endolaser photocoagulation. The patient underwent indirect argon blue-green laser photocoagulation under a retrobulbar lidocaine hydrochloride block. Because of the hazy ocular media, increased laser power settings were needed to produce retinal burns. The retinal break was treated with 206 laser spots of 200-μm spot size at 750- to 1,000-mW power at 0.2 second. Immediately after the treatment, some bubbles were noticed on the back surface of the intraocular lens. Slit-lamp examination confirmed the vacuoles in the posterior capsule, which coalesced and left a 4.5-mm large oval capsulotomy in the supranasal quadrant of the posterior capsule (Figure). The intraocular lens implant remained stable and no vitreous herniation into the anterior chamber was evident. Follow-up examination at six weeks disclosed 20/100 visual acuity with a stable intraocular lens implant and a flat retina.

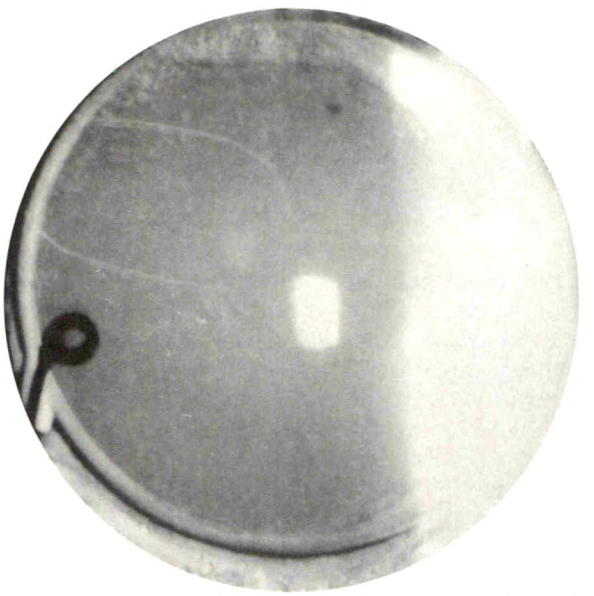


Figure (Lakhanpal, Husain, and Schocket). Case 2. Slit-lamp photograph showing a well-circumscribed, oval, posterior capsulotomy in the superonasal quadrant.

Discussion

The indirect ophthalmoscope delivery system differs from the slit-lamp delivery system. The power and spot size delivered to the retina with the indirect system vary, depending on the following factors. The spot size varies with the distance of the surgeon from the patient, the power and tilt of the hand-held lens, and the refractive status of the treated eye.[4] Another drawback of this system is that the plane of focus of the laser spot may inadvertently change because of the movement of the surgeon's head or hand-held lens.[4] Both of our patients were pseudophakic and indirect laser treatment using krypton and argon laser resulted in a well-demarcated, smooth posterior capsulotomy in each patient. The anatomic location of the posterior capsulotomy in each patient corresponded to the direction of the laser beam that traveled to the retinal tear. We believe this complication developed because of the higher laser power settings needed to make adequate chorioretinal burns in eyes with hazy media. Recently operated-on eyes may have hazy media caused by corneal epithelial haze and folds in Descemet's membrane, anterior chamber reaction, deposits on the lens implant, posterior capsular pigmentation and blood, or opacification. In our cases, vitreous haze with a partially air-filled eye after vitrectomy and scleral buckling was responsible for hazy media in one patient, whereas vitreous hemorrhage from peribulbar perforation was responsible in the other patient. The increased laser power settings (300 to 1,000 mW) as well as the increased exposure time setting (0.2 to 0.5 second) may have caused this complication. Additionally, some of the argon blue-green/krypton laser energy may have been absorbed by the blood or pigment on the posterior capsular surface, resulting in capsulotomy.

Vitreoretinal surgeons should be aware of possible accidental posterior capsulotomy during indirect laser photocoagulation of the retina. In pseudophakic patients, a large break in the posterior capsule may lead to instability of the lens, resulting in its dislocation and vitreous herniation into anterior chamber with its sequelae. In both of our cases, the inadvertent capsulotomy was not suspected during the laser treatment. The break in the posterior capsule during laser treatment did not decrease visualization of the fundus. Drack and associates[7] found that laser-induced cataract as a complication during indirect laser photocoagulation may not lead to decrease in fundus visualization. They found that the anterior subcapsular lens opacities in their patients were only recognized during portable slit-lamp examination after the laser treatment. This contrasts with a previous report of photocoagulation-induced lens opacities with the argon laser slit-lamp delivery system in which the ocular media continued to worsen with increasing laser-induced cataracts.[8]

Because this complication may develop without warning, its prevention is important. Careful preoperative slit-lamp examination should be performed to look for any capsular opacification, blood, or pigment. In cases in which higher laser energy is needed for treatment in hazy media, increasing the laser power setting while decreasing the exposure time may help to prevent this complication. Periodic slit-lamp examination during and after treatment is recommended.

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Polymerase Chain Reaction for the Detection of the Varicella-zoster Genome in Ocular Samples From Patients With Acute Retinal Necrosis

Mauro Nishi, M.D., Rodolfo Hanashiro, M.D., Shigeo Mori, M.D., Kanjiro Masuda, M.D., Manabu Mochizuki, M.D., and Ryo Hondo, Ph.D.

We used the polymerase chain reaction to detect the virus genome in ocular samples from patients with clinically diagnosed acute retinal necrosis. Four samples from four patients with acute retinal necrosis, and five samples from three patients with other ocular diseases (sarcoidosis, rhegmatogenous retinal detachment, and epiretinal membrane of unknown origin) were evaluated. The samples consisted of aqueous humor, vitreous, or subretinal fluid. Primers were specific for varicella-zoster virus, herpes simplex virus, or cytomegalovirus. The varicella-zoster virus genome was detected in three of the four samples from patients with acute retinal necrosis. Among these three positive samples, two had *Pst*I-site-less point mutation, strains that have been described only in Japan and of low prevalence. Samples from patients with diagnoses other than acute retinal necrosis yielded negative results when varicella-zoster virus primer was used. No sample was positive for herpes simplex virus or cytomegalovirus primers.

ACUTE RETINAL NECROSIS is characterized by retinal vasculitis, necrotizing retinitis, vitreous opacities, and iridocyclitis occurring in otherwise healthy individuals.[1] Varicella-zoster virus and herpes simplex virus type 1 have been isolated from ocular specimens from patients with acute retinal necrosis,[2,3] and were presumed to be the cause in those cases.

Acute retinal necrosis is commonly diagnosed on the basis of clinical features, with occasional corroborative information by laboratory techniques, such as demonstration of virus-specific cellular antigens,[4,5] detection of virus-induced serum or intraocular antibodies,[6-10] or visualization of histologic changes in the infected tissue.[11-13] Titration of serum antibodies against the herpesvirus family is more commonly used, but levels are frequently insufficient for conclusive diagnosis.[14]

We investigated the potential use of the polymerase chain reaction, a new and sensitive technique, for the investigation of the viral origin of cases clinically diagnosed as acute retinal necrosis. The polymerase chain reaction consists of repetitive cycles of DNA synthesis, after binding of specific oligonucleotide primers to the DNA from the sample being studied.[15] With each cycle, there is an almost doubling of the final desired DNA product, so that a millionfold amplification is possible. This powerful method has made possible the diagnosis of acute retinal necrosis from extremely small samples, such as can be obtained from the aqueous humor. After detection of the varicella-zoster virus genome in these ocular specimens, we used the *Pst*I restriction endonuclease for varicella-zoster virus strain differentiation.

Patients and Methods

Intraocular samples—The patient data and specimens used for polymerase chain reaction were evaluated (Table). One specimen from

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From the Department of Ophthalmology, Escola Paulista de Medicina, São Paulo, Brazil (Dr. Nishi); Department of Ophthalmology, School of Medicine (Drs. Nishi, Hanashiro, and Masuda), and Department of Pathology, Institute of Medical Research (Drs. Mori and Hondo), the University of Tokyo, Tokyo, Japan; Department of Microbiology, Institute of Public Health, Tokyo, Japan (Dr. Hondo); and Department of Ophthalmology, School of Medicine, Kurume University, Kurume, Japan (Dr. Mochizuki). This study was supported in part by the Japanese Ministry of Education, Science and Culture, Tokyo, Japan (Dr. Nishi); and the Brazilian National Council of Scientific and Technological Development, Brasilia, Brazil (Conselho Nacional de Desenvolvimento Científico e Technológico) (Dr. Nishi).

Reprint requests to Mauro Nishi, M.D., Doheny Eye Institute, 1355 San Pablo St., Los Angeles, CA 90033.

TABLE
PATIENT DATA AND SPECIMENS SUBMITTED FOR POLYMERASE CHAIN REACTION

PATIENT NO., AGE (YRS), GENDER	CLINICAL DIAGNOSIS	SPECIMEN USED	EXTRACTED DNA (NG/μL)
1, 35, M	Acute retinal necrosis	Vitreous membrane	42.5
2, 80, M	Acute retinal necrosis	Vitreous	70.0
3, 41, M	Acute retinal necrosis	Aqueous humor	12.5
4, 22, M	Acute retinal necrosis	Aqueous humor	< 5.0
5, 23, M	Sarcoidosis	Vitreous	ND*
6, 19, M	Retinal detachment	Aqueous humor	32.5
		Subretinal fluid	15.0
7, 60, F	Epiretinal membrane	Epiretinal membrane	10.0
		Vitreous	57.5

*ND indicates test not done.

each of the four patients with a clinical diagnosis of acute retinal necrosis was used in our study. These patients were all previously healthy individuals who developed retinal vasculitis, confluent necrotizing retinitis, and vitreous opacities. Sera were collected within one week of the onset of the symptoms and monthly thereafter. Five intraocular specimens from three patients with clinical diagnoses other than acute retinal necrosis were used as controls for the polymerase chain reaction. Approximately 0.1 ml of aqueous humor was obtained by anterior chamber paracentesis by using a 27-gauge needle. Vitreous and subretinal fluid specimens were collected during surgical procedures, so the volumes obtained were disparate. These specimens were preserved at −20 C until use.

DNA extraction—The specimens were centrifuged for one hour at 25,000 rpm, and the pellets were resuspended (total volume, 400 μl) in 10-mmol/l Tris-HCl (pH 8.0), 10-mmol/l ethylenediaminetetraacetic acid (EDTA), 0.1-mol/l NaCl, and 0.6% sodium dodecyl sulfate. Proteinase K, 200 μg/ml, was added to the solution, which was incubated for two hours at 37 C. The solution was mixed with an equal volume of phenol, followed by collection of the aqueous phase. This procedure was conducted twice, after which it was repeated by using chloroform. Deoxyribonucleic acid precipitation was effected by adding 10 μl of 5-mol/l NaCl and 2.5 volumes of cold 100% ethanol. The extracted DNA was resuspended in 2-mmol/l Tris-HCl (pH 7.8), 0.2-mmol/l EDTA, and 2-mmol/l NaCl. The concentration of DNA in each sample was determined by using spectrophotometric readings at a 260-nm wavelength.[16]

Polymerase chain reaction—Ten microliters of sample-extracted DNA was amplified in a 100-μl reaction mixture that contained 10-mmol/l Tris-HCl (pH 8.4), 50-mmol/l KCl, 1.5-mmol/l $MgCl_2$, 0.01% gelatin, 200 μmol/l each of all four deoxyribonucleoside triphosphates, 2.5 units of Taq polymerase, and 1 μmol/l each of two oligonucleotide primers. The varicella-zoster virus primers, described by Hondo and associates,[17] have the following sequences: sense oligo-5′-TTCAGCCAACGTGCCAATAA A-3′, and antisense oligo-5′-GTTACTTCCG TTAAGCGCGTC-3′. These primers were used to amplify a 642-bp target sequence that is incorporated in the *Eco*RI-D fragment of the varicella-zoster virus genome.[18] Primers specific for herpes simplex virus and for cytomegalovirus were also used in the polymerase chain reaction. The polymerase chain reaction amplification, in an automated DNA thermal cycler, consisted of 50 cycles at 94 C for one minute (denaturation), 55 C for two minutes (annealing), and 72 C for three minutes (extension). Ten microliters of the polymerase chain reaction product were loaded into the slots of a 1.5% horizontal agarose gel in buffer (40-mmol/l Tris-base; 5-mmol/l sodium acetate; 1-mmol/l EDTA, pH 7.6) and run at 75 mA for 55 minutes; one slot was occupied by a DNA molecular-weight marker that presented fragment sizes equal to 587, 434, and 267 bp, as determined by computer analysis of the sequence from plasmid pBR 322 DNA digested by restriction enzyme *Hind*-III.[19] The gel was prepared with ethidium bromide, 0.5 μg/ml, and photographs were taken on an ultraviolet light transilluminator. After agarose gel electrophoresis, we used microplate hybridization[20,21] for the specific identification of the amplified DNA observed in some specimens when varicella-zoster virus primers were used. The remaining polymerase chain reaction product was purified with phenol, chloroform, and ethanol as described previously. These purified deoxyribonucleic acids were adsorbed to Maxisorp microplatewells(Nunc,Roskilde,Denmark)inthepresence of 1.5-mol/l NaCl. The immobilized DNA was hybridized with a biotin-labeled DNA probe, and the hybridization signal was detect-

ed by streptavidin-conjugated β-galactosidase.

Standard strategy was followed to avoid false-positive findings caused by polymerase chain reaction product carryover.[22] The polymerase chain reaction mixture was prepared in a laminar flow hood equipped with ultraviolet lights that were turned on whenever the hood was not in use. The area reserved for manipulation of samples and reagent before polymerase chain reaction was physically isolated from the area of polymerase chain reaction and postamplification manipulation. Buffer solutions used in polymerase chain reaction were divided into aliquots and were autoclaved. Positive-displacement pipettes with disposable tips were used for polymerase chain reaction mixture preparation. Tips that feature an inert bonded fiber barrier to avoid aerosol cross-contamination were used for pipetting in other procedures. Negative controls in each set of amplification consisted of reagents in which the specimen's DNA was substituted by buffer.

Restriction endonuclease analysis—The amplified target sequence DNA for varicella-zoster virus was confronted with *Pst*I restriction endonuclease (Toyobo Co., Tokyo, Japan). The digestion process followed the conditions recommended by the suppliers. The varicella-zoster virus strain that has the *Pst*I cleavage pattern exhibits two bands of 286 bp and 356 bp, after digestion with *Pst*I.

Results

Only Patient 1 had a marked increase in serum indirect immunofluorescent IgG antibody titers, first demonstrable one month after onset of symptoms, against varicella-zoster virus (>1:4, 1:32), herpes simplex virus (1:8, 1:64), and cytomegalovirus (1:32, 1:128).

The different concentrations of DNA extracted from the specimens in our study were evaluated (Table).

Hondo and associates[17] demonstrated that the varicella-zoster virus primers used in our experiment produce a specific single band in the ethidium bromide–stained agarose gel when the varicella-zoster virus genome is used as a template in the polymerase chain reaction amplification. The homogeneous size of the products indicated that rare "mispriming" occurred, and that a band at the expected size would be an unlikely false-positive finding. Deoxyribonucleic acid bands of the size expected to be amplified from the varicella-zoster virus genome were seen on gel electrophoresis in samples from Patients 1, 3 (Figure), and 4, each of whom had a clinical diagnosis of acute retinal necrosis. No specific DNA band was detected in the specimen from Patient 2, or in specimens from the patients with diseases other than acute retinal necrosis. Each experiment was

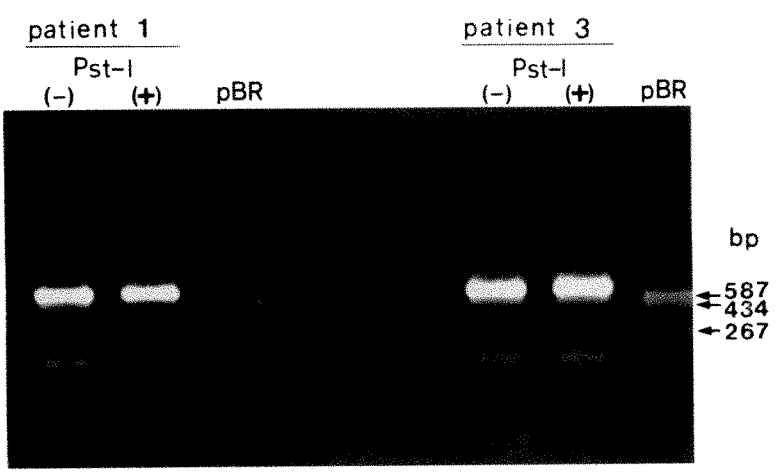


Figure (Nishi and associates). Agarose gel electrophoresis of polymerase chain reaction products from two samples of a patient with clinical diagnosis of acute retinal necrosis. Analysis of *Pst*I restriction endonuclease was also performed. Deoxyribonucleic acid extracted from the vitreous membrane of Patient 1 and the aqueous humor sample of Patient 3 (and Patient 4, not shown) had an amplification product compatible with the varicella-zoster virus genome target sequence (642 bp), as observed in the lane in which *Pst*I was not introduced. When *Pst*I was introduced, the samples from Patient 1 and 3 had a *Pst*I noncleavage pattern observed in 25% of the varicella-zoster virus strains in Japan. The plasmid pBR 322 DNA digested by restriction enzyme *Hind*-III was used as molecular-weight standards that had fragment sizes equal to 587, 434, and 267 bp.

repeated at least twice to confirm the results. The specificity of these polymerase chain reaction results was confirmed by using a varicella-zoster probe in microplate hybridization. No herpes simplex virus or cytomegalovirus DNA was detected in any specimen tested.

The amplified varicella-zoster virus deoxyribonucleic acids were analyzed by *Pst*I restriction endonuclease. Two of the three varicella-zoster virus deoxyribonucleic acids detected represented a virus strain that carried a *Pst*I-site-less mutation (Figure). The sample from Patient 4 had a *Pst*I cleavage pattern.

Discussion

Varicella-zoster virus isolation from intraocular material of an eye enucleated during the acute phase of the acute retinal necrosis syndrome has been described,[8] but in most instances, virus culture of intraocular specimens for clinical diagnosis of acute retinal necrosis is not practical. The small quantities of intraocular fluid obtained are probably not adequate for virus isolation, and these tests usually require days or weeks before results can be reported. Additionally, although virus culture is a sensitive technique for the diagnosis of most infections caused by herpes simplex virus and cytomegalovirus, it is usually insensitive for the diagnosis of varicella-zoster virus infection.[23,24] Accordingly, an indirect method, such as the detection of antibody response, is more commonly used for virus identification in acute retinal necrosis. Unfortunately, serum levels of a specific antibody may not represent localized ocular infection, and an increase in serum titer of virus antibodies has not been observed in some cases of acute retinal necrosis, even though definitive virus isolation from intraocular fluid could be accomplished.[2,14] Pepose and associates,[14] in reviewing the published reports, noted that only 13 of 33 patients with acute retinal necrosis had a diagnostic change in herpesvirus antibody levels on serial sampling. In our study, we detected an increase in the antibody titers for not only varicella-zoster virus, but also for herpes simplex virus and cytomegalovirus, concomitantly. These increases in antibody titers were found in one patient with a diagnosis of acute retinal necrosis whose intraocular sample contained the varicella-zoster virus genome, as recognized by the polymerase chain reaction.

Usui, Hasemi, and Onishi[25] found increased varicella-zoster virus antibody titers in vitreous samples as compared to serum samples in four cases of acute retinal necrosis. Using this criterion, a review of the published reports has shown considerable positivity when paired sera and intraocular samples were processed for antibodies against the herpes-family virus.[14] But only few cases included in this review have followed the standard Witmer coefficient[26] that would demonstrate intraocular antibody production, as opposed to a breakdown of the blood-retina barrier. Even in cases in which intraocular antibody production is suggested, it is always possible that high intraocular titers may reflect a nonspecific polyclonal activation of B cells in an inflammatory process.

The use of monoclonal antibodies to identify the antigen of the herpes-family virus provides rapid diagnosis, but not infrequently has been insensitive. The presence of local antibody may block virus-specific antigens, or the small quantity of obtainable sample may limit the usefulness of this diagnostic method.

The use of retinal biopsy to diagnose acute retinal necrosis by histologic changes has been described,[19] but this seems to be a potential source of iatrogenic complications.

Using the polymerase chain reaction, we identified the varicella-zoster virus genome in three of four samples from patients with clinically diagnosed acute retinal necrosis. Even though varicella-zoster virus is a ubiquitous virus, five specimens from three patients with diagnoses other than acute retinal necrosis did not yield this finding. This result suggests that the detection of the varicella-zoster virus genome in the intraocular material is directly related to the etiopathogenicity of acute retinal necrosis in these cases.

Among samples from patients with clinically diagnosed acute retinal necrosis, only Patient 2 did not have positivity for varicella-zoster genome tested by polymerase chain reaction and microplate hybridization. In addition to the suggestion that varicella-zoster DNA was not present in the sample of Patient 2, it is also conceivable that DNA extraction was inadequate; however, we used a standard method of DNA extraction, the efficiency of which is currently accepted. The evaluation of DNA concentration for each sample, using spectrophotometry, showed that specimens from Patient 2 had the highest amount of extracted DNA among all samples evaluated in our study (Table). The sample from Patient 2 was collected four months after onset of disease, when no

active infection was apparent and treatment with acyclovir had been completed. Possibly, in the late stage of the disease, few or no infected cells were retained in the collected vitreous.

Acute retinal necrosis exerts its damaging effects on the posterior pole structures. Nevertheless, we were able to detect the varicella-zoster virus genome in the aqueous humor, where virus would be expected to be scarce. These samples were collected in an active stage of the disease, less than one month after onset of symptoms. Because the polymerase chain reaction is such a sensitive technique, minute samples, such as 0.1 ml of aqueous humor, are sufficient for diagnosis.

The use of aqueous humor to diagnose acute retinal necrosis has great clinical implications because of the ease with which aqueous humor can be obtained, unlike the vitreous, which entails a surgical procedure. For this reason acute retinal necrosis can be diagnosed in the early stages of the disease process, and appropriate treatment can be initiated more promptly.

Contamination is a great concern when the polymerase chain reaction is used. Standard strategies to avoid contamination caused by polymerase chain reaction product carryover[22] were applied. Additionally, the samples with diagnoses other than acute retinal necrosis also guaranteed that the appropriate technique was being used. The varicella-zoster virus primers used in our study were developed by Hondo and associates,[17] and did not amplify homologous genomic sequences in herpes simplex virus, cytomegalovirus, or human chromosomal DNA. They amplified a single band of 642-bp oligonucleotide that hybridized with the biotinylated DNA probe.[20]

After detection of the varicella-zoster virus genome, we used a *Pst*I restriction endonuclease to differentiate two substrains. Among three cases that were positive for varicella-zoster virus, two lacked a *Pst*I cleavage site. An epidemiologic study conducted by Hondo and associates[18] found the *Pst*I-site-less mutation in 25% of the strains of varicella-zoster virus seen in Japan, but this mutation is not common outside Japan.

Acute retinal necrosis was first described by Urayama, Yamada, and Sasaki,[27] and subsequent Japanese published reports[28,29] have shown a relatively high incidence of this entity in Japan, which suggests a native strain of virus, perhaps with a high neurovirulence, is responsible for acute retinal necrosis in Japan. Whether the *Pst*I-site-less mutation is a marker of a highly virulent virus is still obscure. However, future use of the polymerase chain reaction to identify the substrain of virus that causes acute retinal necrosis may provide some clues to its physiopathologic characteristics, which may result in better therapy.

The polymerase chain reaction has already been used to demonstrate cytomegalovirus DNA in intraocular samples from immunosuppressed patients,[30] and to identify herpes simplex virus in normal corneas and in corneal epithelium with clinically apparent herpes keratitis.[31] Epstein-Barr virus DNA has been detected in samples from patients with Sjögren's syndrome.[32,33] Primers for the previously mentioned herpes-family viruses are now widely available, but this is not yet true for varicella-zoster virus. The strongly cell-associated replication of varicella-zoster virus in vitro has made the preparation of cell-free virions difficult and time consuming. Consequently, varicella-zoster virus is the least well characterized of the human herpes viruses.[34]

Although specific primers for herpes simplex virus and cytomegalovirus were used in our study, no evidence of the deoxyribonucleic acids of these viruses was detected. There have been several reports of increased intraocular antibodies to herpes simplex virus type I in the aqueous humor of patients with acute retinal necrosis,[5,24] as well as isolation of herpes simplex virus type I from intraocular samples.[3] This implies that numerous herpes-family viruses can cause clinically similar ocular disease by inducing a necrotic retinitis. With the use of the polymerase chain reaction, more definitive etiologic diagnosis of acute retinal necrosis would be possible, and clinical distinctions may become apparent. Identification of the specific causative agent has significant therapeutic relevance, in that herpes simplex is sensitive to acyclovir, whereas herpes zoster is sensitive only at a higher dose.[35] Cytomegalovirus, conversely, is resistant to acyclovir, but is sensitive to ganciclovir and foscarnet.[36] Accordingly, a method such as polymerase chain reaction that can clearly distinguish between these possible viral origins would have an important role in the successful management of fulminant and destructive entities, including acute retinal necrosis.

Our results suggest that the detection of varicella-zoster virus DNA by polymerase chain reaction provides useful information for the diagnosis, identification of subtype strains in-

volved in the process, and direction for proper treatment of the acute retinal necrosis syndrome.

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OPHTHALMIC MINIATURE

We are still living under the banner of medieval technology. For instance, eyeglasses were a medieval invention, as important as the mechanical loom or the steam engine. At that time, an intellectual who became farsighted at the age of forty (bear in mind the difficulty of reading unreadable manuscripts by torchlight in dark rooms beneath shadowy vaults) was unable to produce actively after the age of fifty. With the introduction of eyeglasses intellectual productivity increased enormously and the following centuries could better exploit these human resources.

Umberto Eco, *Travels in Hyper Reality*
San Diego, Harcourt Brace Jovanovich, 1990, pp. 64–65

Retained Lens Fragments After Phacoemulsification Manifesting as Marked Intraocular Inflammation With Hypopyon

W. David Irvine, M.D., Harry W. Flynn, Jr., M.D., Timothy G. Murray, M.D., and Patrick E. Rubsamen, M.D.

We reviewed the medical records of four patients with marked intraocular inflammation and hypopyon as the initial manifestation of retained lens fragments after phacoemulsification. The severe inflammatory reaction occurred between one month and one year after the cataract extraction. All four patients underwent pars plana vitrectomy to remove the lens fragments. The vitreous specimens were cultured to rule out infectious endophthalmitis. In all patients, no organisms were isolated from the vitrectomy specimens placed on both aerobic and anaerobic media. All patients had improved vision and resolution of the marked intraocular inflammation after vitrectomy. Echography was useful in establishing the diagnosis in these uncommon cases.

RETAINED LENS FRAGMENTS after extracapsular cataract surgery is an uncommon but potentially serious complication.[1-3] The rise in the percentage of cataract extractions performed with phacoemulsification techniques has been associated with an apparent increase in the incidence of retained lens fragments. Retained lens fragments can produce significant intraocular inflammation, which may lead to secondary glaucoma, media opacities, and cystoid macular edema.[1-3]

Recent reports have described the initial clinical signs, management options, and visual acuity outcomes associated with retained lens fragments.[1-3] We treated four patients with retained lens fragments after phacoemulsification manifesting as marked intraocular inflammation and hypopyon.

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From the Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami School of Medicine, Miami, Florida.

Reprint requests to Harry W. Flynn, Jr., M.D., Bascom Palmer Eye Institute, P.O. Box 016880, Miami, FL 33101.

Patients and Methods

The medical records of all patients seen at our institution with retained lens fragments after phacoemulsification during the calendar year 1991 were reviewed. All patients were referred by anterior segment surgeons for management of secondary complications associated with the retained lens fragments. Four patients were identified who had marked intraocular inflammation and hypopyon as the initial clinical manifestations of retained lens fragments. These patients had clinical signs and symptoms similar to postoperative endophthalmitis.

Case Reports

Case 1

A 74-year-old man was examined by us four weeks after cataract extraction with phacoemulsification, anterior vitrectomy, and posterior chamber intraocular lens implantation in the right eye. The referring physician reported that several lens fragments were dislocated posteriorly during the operative procedure. The patient was treated with topical prednisolone phosphate 1% and diclofenac sodium 0.1%, and achieved a visual acuity of 20/30 one week postoperatively. The intraocular inflammation increased over the next three weeks, and visual acuity decreased despite continuation of frequent topical corticosteroids. The patient was referred for treatment of possible infectious endophthalmitis vs sterile inflammation secondary to retained lens material.

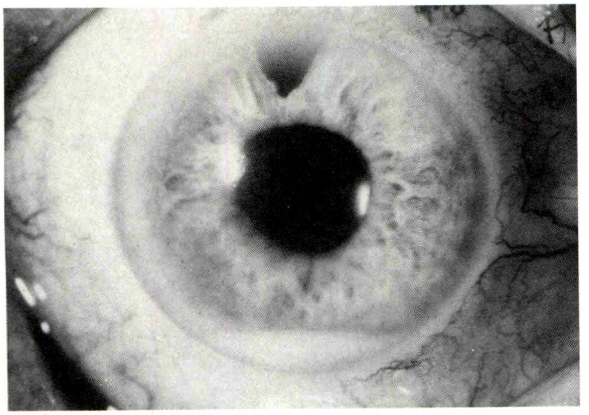


Fig. 1 (Irvine and associates). Case 1. The anterior segment shows marked intraocular inflammation with hypopyon four weeks after phacoemulsification with posteriorly dislocated lens fragments.

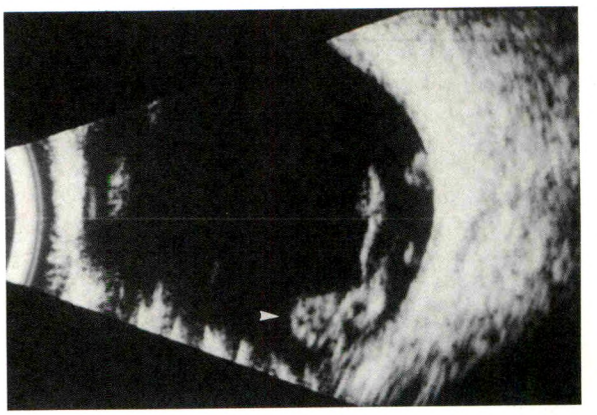


Fig. 2 (Irvine and associates). Case 2. The echogram demonstrates multiple highly reflective opacities consistent with retained lens fragments (arrow).

The examination of the operated-on right eye disclosed a best-corrected visual acuity of 2/200. The tension by applanation was 15 mm Hg. The limbal wound was intact. There was diffuse corneal edema, marked anterior chamber cells and flare, and a hypopyon (Fig. 1). There was a well-positioned posterior chamber intraocular lens. The posterior segment examination disclosed a dense vitreitis with no view of fundus details. The fellow eye was phakic with a moderate nuclear sclerotic cataract and was otherwise unremarkable. Echography demonstrated the presence of multiple highly reflective opacities in the vitreous cavity, consistent with retained lens fragments (Fig. 2).

On the following day, the patient underwent a three-port pars plana vitrectomy with removal of the retained lens fragments from the right eye. Culture results of the vitrectomy specimen were negative on both aerobic and anaerobic media. The visual acuity returned to 20/50 with minimal residual intraocular inflammation one month after the vitrectomy. The intraocular pressure was 16 mm Hg in the right eye.

Six weeks after the vitrectomy, a retinal detachment involving the macula occurred in the right eye. Retinal reattachment was achieved surgically, but the visual acuity remained 20/300 over a follow-up of eight months. An epiretinal membrane involving the macula is present.

Case 2

A 74-year-old woman underwent cataract extraction with phacoemulsification in the right eye one year before referral to us. The cataract operation was complicated by posterior capsule rupture and dislocation of lens fragments posteriorly. An anterior chamber intraocular lens was inserted. Postoperatively, the patient had persistent intraocular inflammation that was treated with topical corticosteroid drops. The best postoperative visual acuity three months after the cataract operation was recorded as 20/60. At 11 postoperative months, the patient discontinued her topical corticosteroids. One month later, the patient had a progressive decrease in visual acuity associated with the increasing intraocular inflammation.

Our initial examination of the right eye disclosed a visual acuity of hand motions. The tension by applanation was 17 mm Hg. Diffuse corneal edema and folds in Descemet's membrane were present. There was moderate anterior chamber inflammation and a hypopyon. The anterior chamber intraocular lens was well positioned. The posterior segment examination disclosed a dense vitreitis with a limited view of fundus details. The fellow eye was phakic with a moderate nuclear sclerotic cataract. Echography demonstrated multiple highly reflective vitreous opacities consistent with retained lens fragments.

The patient was initially treated with hourly topical prednisolone acetate 1% drops and had minimal improvement. Four days later, the patient underwent a three-port pars plana vitrectomy with removal of the retained lens fragments from the right eye. Culture results of the vitrectomy specimen were negative on both aerobic and anaerobic media.

The intraocular inflammation resolved, and seven months after vitrectomy, the visual acuity was 20/40 and tension was 23 mm Hg.

Case 3

An 85-year-old man had severe pain and poor vision in the right eye eight weeks after cataract extraction with phacoemulsification. No history was available from the cataract surgeon, and the patient was not aware of any complications during the surgery.

Examination of the operated-on eye disclosed a visual acuity of hand motions and a tension by applanation of 23 mm Hg. There was significant conjunctival injection, chemosis, and purulent discharge. The cornea demonstrated moderate diffuse edema and folds. There was a severe anterior chamber inflammatory reaction with hypopyon. An anterior chamber intraocular lens was present. The posterior segment examination disclosed a dense vitreitis with no view of posterior pole details. The fellow eye was phakic with a moderate nuclear sclerotic cataract but was otherwise unremarkable. Because of the large hypopyon and marked pain, postoperative endophthalmitis was suspected. However, with the evidence of complicated cataract extraction, including the presence of an anterior chamber intraocular lens, sterile inflammation secondary to retained lens material was also included in the differential diagnosis. Echography was performed and disclosed multiple lens fragments, including a large intact portion of the nucleus in the posterior vitreous cavity (Fig. 3).

A three-port pars plana vitrectomy was performed with removal of the retained lens nucleus. Intraoperatively, a peripheral retinal tear and localized retinal detachment were noted. A scleral buckling procedure, cryoretinopexy, and fluid-gas exchange were performed during the same operative procedure. Specimens of aqueous and vitreous were sent for culture and intraocular antibiotics (vancomycin HCl, 1 mg; amikacin, 0.2 mg) and 0.4 mg of dexamethasone were injected. No organisms were isolated on aerobic and anaerobic culture media.

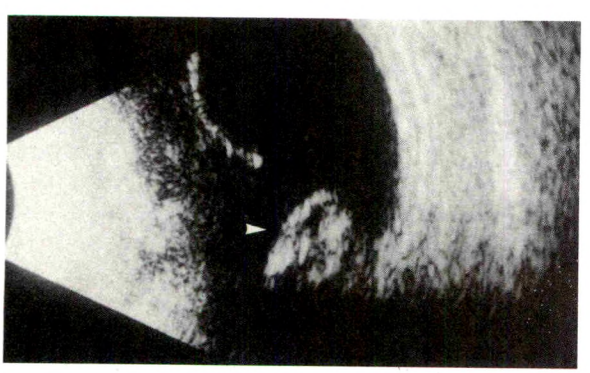


Fig. 3 (Irvine and associates). Case 3. The echogram demonstrates a large intact portion of retained lens nucleus (arrow).

Postoperatively, the intraocular inflammation resolved and the retina remains attached. Visual acuity was 20/400 and tension was 18 mm Hg at the two-month follow-up examination.

Case 4

A 90-year-old woman underwent cataract extraction with phacoemulsification in the left eye five months before our initial examination. Postoperatively, vision failed to improve and the patient was aware of a large floater in the left eye. Additionally, she gave a one-month history of increased intraocular pressure. Her medical regimen included topical prednisolone acetate 1% every four hours and betaxolol 0.5% twice daily. The patient was referred because of persistent intraocular inflammation and the suspicion of an inferior retinal detachment.

Our examination of the left eye disclosed a visual acuity of 5/200. The tension by applanation was 16 mm Hg. The limbal wound was intact. There was diffuse corneal edema. There was marked anterior chamber cell and flare with a 10% hypopyon. An anterior chamber intraocular lens was well positioned. Examination of the posterior segment disclosed a moderate vitreitis with no evidence of retinal detachment. Through the hazy media, multiple tiny lens fragments and a large segment of the nucleus were observed in the inferior vitreous. The fellow eye was pseudophakic. Cataract extraction had been performed one month before the procedure in the left eye.

The patient was maintained on a regimen of topical prednisolone acetate 1% every two hours with no improvement. Three days later, a pars plana vitrectomy with removal of the retained lens fragment was performed on the right eye. Cultures of the vitrectomy specimen were negative on both aerobic and anaerobic media.

Three months after vitrectomy, the visual acuity had returned to 20/40 with no residual

intraocular inflammation. The tension by applanation was 12 mm Hg.

Discussion

Lens-induced intraocular inflammation is a well known sequela to spontaneous, surgical, or accidental interruption of the lens capsule.[1-4] The degree of induced inflammation can be highly variable. In some cases, the lens material may appear to be relatively inert, thus causing minimal reaction. In other cases a marked inflammation response causes significant media opacities and hypopyon, as in these four cases.

Severe lens-induced inflammation with hypopyon formation after cataract extraction is an uncommon occurrence. Smith and Weiner[5] described one case of marked intraocular inflammation with hypopyon after phacoemulsification in a patient who had undergone extracapsular cataract extraction in the fellow eye five months previously. They concluded that a small amount of residual lens material retained anteriorly was responsible for the severe inflammatory reaction. Hutton, Snyder, and Vaiser[3] described a sterile hypopyon in one of 26 eyes managed with surgically dislocated intravitreal lens fragments. Their case was associated with a retained lens nucleus after attempted intracapsular cataract extraction. Fastenberg and associates[2] described one patient with hypopyon and marked inflammation five weeks after phacoemulsification with dislocated lens fragments in their series of 13 patients.

Postoperative severe intraocular inflammation with hypopyon formation in a patient is typical for infectious endophthalmitis. The differential diagnosis includes severe acute iridocyclitis, retained intraocular foreign bodies, inflammation induced by intraocular medications including many topical anesthetics, as well as a reaction to lens protein.[6] Even with a history of retained lens fragments, as was provided in three of our four cases, it is often difficult to rule out coexisting infectious endophthalmitis. The vitrectomy specimens were evaluated on both aerobic and anaerobic media in all patients. We injected intraocular antibiotics in one of our patients (Case 3) because of uncertainty in the clinical diagnosis. It was our clinical impression that the inflammation was lens-induced in the other three patients, and no intraocular antibiotics were given.

The time of onset of the severe inflammatory reaction in our four patients varied from relatively early (one month) to late (one year) after the cataract extraction. None of these cases occurred in the acute postoperative period (within one week) as is most common with postoperative infectious endophthalmitis. Delayed-onset and recurrent pseudophakic endophthalmitis secondary to indolent organisms such as *Propionibacterium acnes*, *Candida* species, *Corynebacterium* organisms, and *Staphylococcus epidermidis* has been described.[7] In these four cases, no organisms were isolated on either aerobic or anaerobic culture media, which were observed for at least 14 days. Additionally, the severe intraocular inflammation resolved in all four patients after vitrectomy with removal of the retained lens fragments.

In three of our four cases, echography was instrumental in establishing or confirming the presence of retained lens fragments. This information was useful in guiding our therapeutic decisions. For example, in Case 3 the patient had no history of retained lens material and the marked intraocular inflammation was initially thought to be the result of infectious endophthalmitis. However, the performance of vitreous tap for culture and injection of intraocular antibiotics, a common approach for infectious endophthalmitis, would clearly have been ineffective in eyes with lens-induced inflammation. With ultrasound confirmation of a large piece of retained lens nucleus, the need for pars plana vitrectomy with removal of the lens material became obvious.

Marked intraocular inflammation with hypopyon formation can manifest in eyes with retained lens fragments after cataract extraction. With the apparent increase in the number of surgically dislocated lens fragments after phacoemulsification, an increased awareness of this clinical entity is necessary. In this small series, we were unable to distinguish between the inflammation induced by the nuclear material and that of the cortical fragments. The diagnosis can often be made by a detailed history, careful clinical examination for evidence of complications from the preceding cataract extraction, and echography. In typical cases as described in this series, intraocular cultures should be obtained at the time of vitrectomy but intraocular antibiotics may be

withheld until the culture results or clinical course indicate an infectious cause.

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OPHTHALMIC MINIATURE

Leprosy is not a disease that kills in short days. It is slow. Emmanuel's condition was changing when the disease showed around his eyes. He was looking then like a cow with large white or brown spots around its dark eyes. About that time, visitors to his hut began to be less.

Don Bloch, *The Modern Common Wind*
London, Paladin Grafton Books, 1985, p. 30

Vogt-Koyanagi-Harada Syndrome in Patients With Cherokee Indian Ancestry

Jose A. Martinez, M.D., Pedro F. Lopez, M.D., Paul Sternberg, Jr., M.D., Thomas M. Aaberg, M.D., H. Michael Lambert, M.D., Antonio Capone, Jr., M.D., Barry A. Mandell, M.D., and Nancy J. Newman, M.D.

Eight patients with Vogt-Koyanagi-Harada syndrome who have Cherokee Indian ancestry ranged from 17 to 49 years of age. Five of the patients were black, three were white. Visual acuity at the time of initial examination ranged from 20/20 to counting fingers. Clinical findings included granulomatous iridocyclitis in six patients, vitreitis in seven patients, disk edema in five patients, exudative retinal detachment in six patients, and multifocal choroidal lesions in all eight patients. All of the patients were treated with systemic corticosteroids, and they recovered visual acuity of 20/40 or better. The seven patients assayed had the HLA-DRw52 haplotype, including five who were homozygous for this allele. This finding may add to the increasing evidence that a class II HLA antigen at a D-related locus may predispose carriers to the development of Vogt-Koyanagi-Harada syndrome.

VOGT-KOYANAGI-HARADA SYNDROME is a uveomeningitic disease typically characterized by three of the following features in patients without a history of intraocular surgery or penetrating ocular trauma: (1) bilateral iridocyclitis; (2) posterior uveitis (that is, exudative retinal detachment, choroidal infiltrates, disk edema); (3) central nervous system manifestations (that is, headache, dysacousia, meningismus, cranial nerve palsies, or cerebrospinal fluid pleocytosis); and (4) cutaneous manifestations (that is, poliosis, vitiligo, alopecia).[1] Recently, several articles have focused on the possible linkage between this syndrome and a specific human leukocyte antigen (HLA).[2-5]

We studied the clinical characteristics and HLA type in a group of patients with Vogt-Koyanagi-Harada syndrome who have Cherokee Indian ancestry.

Subjects and Methods

Vogt-Koyanagi-Harada syndrome was diagnosed in eight unrelated patients with Cherokee Indian ancestry. Each patient had a grandparent or great-grandparent who was a full-blooded Cherokee Indian. Six of the eight patients clearly met the diagnostic criteria for Vogt-Koyanagi-Harada syndrome set up by the American Uveitis Society.[1] The other two patients lacked bilateral iridocyclitis but appeared to have the posterior form of the disease often referred to as Harada's disease.

Table 1 summarizes their clinical features. The patients ranged in age from 17 to 49 years. Seven of the patients were female and one was male. Five of the patients were black, and three of the patients were white. Visual acuity at the time of initial examination ranged from 20/20 to counting fingers. All patients initially had decreased vision and headache. Meningismus was present in five patients, and dysacousia was noted in four patients. Clinical findings included granulomatous iridocyclitis in six patients, vitreitis in seven patients, disk edema in five patients, and exudative retinal detachment in six patients. All eight patients had clinically

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From the Department of Ophthalmology, Emory University School of Medicine, Atlanta, Georgia. This study was supported in part by P30 EY06360 (a National Institutes of Health Departmental Core Grant); by a Departmental Grant from Research to Prevent Blindness, Inc., New York, New York; and by a Knapp Fellowship from the Heed Ophthalmic Foundation. Dr. Lopez was a Heed Ophthalmic Foundation Fellow (1990–1991).

Reprint requests to Pedro F. Lopez, M.D., Doheny Eye Institute, University of Southern California School of Medicine, 1450 San Pablo St., Los Angeles, CA 90033..

TABLE 1
CLINICAL FEATURES OF VOGT-KOYANAGI-HARADA PATIENTS WITH CHEROKEE INDIAN ANCESTRY*

PATIENT NO., AGE (YRS), RACE, GENDER	INITIAL VISUAL ACUITY	HEADACHE	STIFF NECK	DYSACOUSIA	IRIDOCYCLITIS	VITREITIS	DISK EDEMA
1, 38, white, F	R.E. 20/80 L.E. 20/200	Yes	Yes	No	Yes	Yes	Yes
2, 33, white, F	R.E. 20/40 L.E. 20/20	Yes	Yes	No	No	Yes	Yes
3, 17, black, M	R.E. 20/200 L.E. 20/200	Yes	No	No	Yes	Yes	Yes
4, 31, black, F	R.E. 20/40 L.E. 20/40	Yes	No	No	Yes	Yes	No
5, 32, black, F	R.E. 20/20 L.E. 20/300	Yes	Yes	Yes	Yes	Yes	No
6, 37, black, F	R.E. CF L.E. CF	Yes	No	Yes	Yes	Yes	Yes
7, 22, white, F	R.E. 20/60 L.E. 20/40	Yes	Yes	Yes	Yes	Yes	Yes
8, 49, black, F	R.E. 20/20 L.E. CF	Yes	Yes	Yes	No	No	No

*CF indicates counting fingers.

detectable choroidal lesions during the active phases of the disease. Cerebrospinal fluid pleocytosis was noted in the four patients who had lumbar puncture. Fluorescein angiography was performed on all eight patients, and disclosed early, patchy choriocapillaris filling, multiple pinpoint areas of leakage, late staining of the disk, and, when present, late pooling of dye in the exudative retinal detachments. Ocular echography performed on five patients disclosed a diffusely thickened choroid with low to medium internal reflectivity by A scan.

Results

All eight patients were treated with systemic prednisone and had subsequent marked improvement in visual acuity. All patients recovered visual acuity of 20/40 or better in both eyes during the follow-up interval of two months to 4½ years.

Patient 3 developed a peripapillary choroidal neovascular membrane in his right eye two years after the acute inflammatory phase of the disease. He was treated with laser photocoagulation and, at last follow-up, had a visual acuity of 20/40 secondary to a posterior subcapsular cataract. Patient 5 had a recurrence of the disease after early corticosteroid withdrawal.

Seven of the eight patients had HLA typing performed. All seven patients had the HLA-DRw52 antigen (Table 2). Five of the seven patients were homozygous for the HLA-DRw52 haplotype. No clinical differences were noted between the patients who were homozygous for HLA-DRw52 haplotype and those who were heterozygous. Other haplotypes that were found in three or more of the seven patients who underwent HLA typing included the following: Bw6 in four patients, A28 in three patients, Bw4 in three patients, DQw2 in three patients, and DR3 in three patients. Two of the seven patients had the HLA-DR4/DRw53/DQw3 haplotype.

A ninth patient was not included in our series because of an episode of ocular trauma. This 29-year-old white woman was referred to the oculoplastics service seven days after suffering a ruptured left globe. At the time of consultation, her visual acuity in the left eye was no light perception. The left eye was enucleated ten days after the injury. One month after enucleation, the patient began having pain in her right eye and a mild subjective change in vision (Snellen visual acuity was 20/20). Examination disclosed choroidal infiltrates. Echo-

TABLE 2
HLA TYPE OF VOGT-KOYANAGI-HARADA PATIENTS WITH CHEROKEE INDIAN ANCESTRY

	PATIENTS†							
HLA*	1	2	3	4	5	6	7	8
DR1	–	+	–	–	–	NP	–	–
DR2	–	–	–	–	–	NP	–	–
DR3	+	–	–	–	+	NP	+	–
DR4	+	–	–	–	–	NP	+	–
DR6	–	+	+	–	–	NP	–	–
DR8	–	–	–	–	–	NP	–	+
DR13	–	–	–	–	–	NP	–	+
DRw6	–	–	–	–	–	NP	–	–
DRw11	–	–	–	+	–	NP	–	–
DRw13	–	–	–	+	–	NP	–	–
DRw52	+	+‡	+‡	+‡	+‡	NP	+	+‡
DRw53	+	–	–	–	–	NP	+	–
DQw1	–	+	–	–	–	NP	–	+
DQw2	+	–	+	–	+	NP	–	–
DQw3	+	–	–	–	–	NP	+	–
DQw6	–	+	–	+	–	NP	–	–
DQw7	–	–	–	+	–	NP	–	+
A1	+	–	–	–	–	NP	+	–
A2	–	–	–	+	–	NP	+	–
A3	–	–	–	–	–	NP	–	–
A6	–	–	–	–	–	NP	+	–
A23	–	–	–	–	+	NP	–	+
A24	–	+	–	–	–	NP	–	–
A28	–	–	+	–	+	NP	–	+
A33	–	+	–	–	–	NP	–	–
A36	–	–	–	–	–	NP	–	–
A51	+	–	–	–	–	NP	–	–
Aw36	–	–	–	+	–	NP	–	–
B8	+	–	–	–	–	NP	+	–
B27	–	+	–	–	–	NP	–	–
B61	–	–	–	–	–	NP	–	+
B65	–	–	–	–	–	NP	–	+
Bw4	–	–	+	+	+	NP	–	–
Bw6	+	–	–	+	+	NP	+	–
Bw42	–	–	–	+	+	NP	–	–
Bw51	–	–	–	–	–	NP	+	–
Bw53	–	–	+	–	–	NP	–	–
Bw57	–	–	+	–	–	NP	–	–
Bw58	–	–	–	+	–	NP	–	–
Bw60	+	+	–	–	–	NP	–	–
Bw63	–	–	–	–	+	NP	–	–

*The order of HLA antigens has been changed for emphasis of relevant haplotypes.

†+ indicates present; – indicates absent; NP, haplotype not performed.

‡Homozygosity (double dose) of this haplotype.

graphy detected diffuse choroidal thickening. Fluorescein angiography was not performed. The diagnosis of sympathetic ophthalmia was clearly of primary concern. Pathologic review of the enucleated eye did not show any choroidal infiltrates, Dalen-Fuchs nodules, or other findings characteristic of sympathetic ophthalmia. Upon further questioning, the patient did have Cherokee Indian ancestry and a two-year history of episodes of headaches associated with visual loss that lasted days to weeks. These episodes of visual loss were present before her accident and would resolve spontaneously. In this patient HLA typing was negative for HLA-A11 but was homozygous for HLA-DRw52. Two months later, both her subjective complaints and the choroidal thickening spontaneously resolved. Our tentative diagnosis in this patient was Vogt-Koyanagi-Harada syndrome.

Discussion

Vogt-Koyanagi-Harada syndrome is characterized by a constellation of clinical findings in patients without prior intraocular surgery or ocular penetrating trauma. These findings typically include bilateral uveitis with associated serous retinal detachments, multifocal choroidal infiltrates, or disk edema, as well as associated central nervous system symptoms of headache, stiff neck, or dysacousia.[1,6] These findings were common in our patients.

Vogt-Koyanagi-Harada syndrome occurs primarily in darkly pigmented individuals, specifically in blacks, Hispanics, Orientals, and American Indians. All of our patients had Cherokee Indian ancestry. Five were black, and three were white. None were Hispanic or Oriental.

Headaches and decreased vision are characteristically found in patients with Vogt-Koyanagi-Harada syndrome who seek ophthalmologic consultation. Other symptoms include periorbital pain, tinnitus, low-grade fevers, and nuchal rigidity.[1,6,7] All of these findings were common in our patients. In the early stages of the disease, cerebrospinal fluid lymphocytic pleocytosis is typically found. All four patients described herein who received a lumbar puncture had pleocytosis. Later in the course of the disease, cutaneous manifestations include poliosis, vitiligo, and alopecia. None of our patients had these changes. The incidence of these cutaneous manifestations, however, has recently decreased, possibly because earlier

systemic corticosteroid therapy may arrest the autoimmune process before detectable skin lesions become evident.[7,8]

Typical fluorescein angiographic features include early, patchy choriocapillary filling, multiple pinpoint areas of leakage at the level of the retinal pigment epithelium, late hyperfluorescence of the disk, and late pooling of dye in the serous retinal detachments.[6] These were common features in our patients.

Ocular echography usually discloses a diffusely thickened choroid with low to medium internal reflectivity by A scan. Serous retinal detachments, scleral or episcleral thickening, and mild vitreous debris can also be detected. Ocular echography is helpful in the differential diagnosis of this condition,[9] as well as in making the diagnosis when there is a poor view of the fundus (cataract, dense vitreitis, and the like). It can also be used to quantitate the degree of choroidal thickening, which may be a useful index for monitoring the response to therapy.

Some authors believe the diagnosis of Vogt-Koyanagi-Harada syndrome can be made based solely on the patient's initial complaints and findings, fluorescein angiographic features, and a limited laboratory evaluation to exclude clinically similar diseases.[7] We believe it reasonable to examine some patients more thoroughly, particularly those in whom prolonged therapy with systemic corticosteroids or other immunosuppressive agents is planned, by obtaining a rapid plasma reagin, fluorescent treponemal antibody absorption, angiotensin converting enzyme, chest x-ray, purified protein derivative, human immunodeficiency virus antibody titer, and by performing a lumbar puncture.

Treatment for Vogt-Koyanagi-Harada syndrome initially consists of oral corticosteroids for a period of weeks to months. All eight of our patients were treated with systemic corticosteroids, and their visual acuity improved. Recurrent symptomatic episodes may occur and are particularly common when corticosteroid therapy is tapered too rapidly. Patient 5 had several such recurrences. Patients with long-term or relapsing episodes that are refractory to corticosteroid therapy may be treated with cyclosporine.[7,10-12]

The long-term visual prognosis for patients with Vogt-Koyanagi-Harada syndrome is generally good. Complications that may occur because of corticosteroid therapy include cataracts and glaucoma. The disease process itself may also lead to subretinal neovascularization membrane formation and pigmentary retinopathy.[7]

Autoimmune mechanisms are thought to play an important role in the pathophysiologic course of Vogt-Koyanagi-Harada syndrome.[8,7,8,13-17] Sakamoto, Murata, and Inomata[15] observed that choroidal melanocytes in Vogt-Koyanagi-Harada patients aberrantly express class II HLA antigens on their surface, which possibly result in the autoimmune targeting of these cells.

HLA typing provides a more precise means than ethnicity of identifying common genetic factors that may be important in disease susceptibility.[2] Certain HLA haplotypes appear to be more frequent within different ethnic populations of Vogt-Koyanagi-Harada patients. In Japanese patients, Ohno[3] reported an association with HLA-DR4, -DRw53, -Dw15, and -Bw54. In Chinese patients, Zhao, Jiang, and Abrahams[4] reported an association with HLA-DR4 and -DRw53. In patients in the United States, Davis and associates[2] reported an association with HLA-DR4 and -DRw53. The strongest association observed in these patients, however, was with HLA-DQw3, an antigen that is in positive linkage disequilibrium with DR4, and with the DR4/Dw3 haplotype. This haplotype was present in two of our patients.

Previous reports showed that a disproportionate number of non-Oriental patients and patients in the United States with Vogt-Koyanagi-Harada syndrome have American Indian ancestry when compared to the general population.[2,18,19] They do not specifically report the HLA findings associated with Vogt-Koyanagi-Harada syndrome in patients from a particular American Indian nation.

The opportunity to examine a sizable ethnoregionally homogeneous patient group is presumably related to our institution's close proximity to what was once the Cherokee Indian nation. None of our patients, however, was a full-blooded Cherokee Indian. Instead, they were two or three generations removed from such an ancestor, meaning their grandparent or great-grandparent was a full-blooded Cherokee Indian. All seven patients who underwent typing had the HLA-DRw52 antigen and five were homozygous for HLA-DRw52. The frequency of the HLA-DRw52 antigen in Cherokee Indians is unique; however, none of our patients were immediate descendants of a full-blooded Cherokee Indian. According to a previous report,[20] the HLA-DRw52 antigen occurs in about 74% of blacks and 48% of whites in the general

population. The likelihood that all seven of our patients with Vogt-Koyanagi-Harada syndrome (four black and three white) would test positive for HLA-DRw52 by chance is 3.3% (0.74 × 0.74 × 0.74 × 0.74 × 0.48 × 0.48 × 0.48). The association of the Vogt-Koyanagi-Harada syndrome with HLA-DRw52 in our population is further strengthened by the high incidence of homozygotes for this HLA haplotype (five of the seven patients tested). This higher than expected rate of occurrence in our patients suggests that either HLA-DRw52 or some other closely linked locus may be associated with Vogt-Koyanagi-Harada syndrome in descendants of Cherokee Indians. It is interesting to note that 12 of 14 Vogt-Koyanagi-Harada patients (86%) with American Indian ancestry (tribe or nation) in the series reported by Davis and associates[2] had the HLA-DRw52 antigen. Combining our data with the report by Davis and associates[2] discloses an HLA-DRw52 incidence of 90% (19 of 21) in Vogt-Koyanagi-Harada patients with American Indian ancestry. The apparently increased incidence of DRw52 in Vogt-Koyanagi-Harada patients with American Indian ancestry suggests a permissive or contributory role of this HLA allele, or other closely linked alleles, in the pathogenesis of Vogt-Koyanagi-Harada syndrome in this population. It is likely that significant differences exist in the specific HLA-DR locus associated with the Vogt-Koyanagi-Harada syndrome in ethnoregionally distinct populations. Zhao, Jiang, and Abrahams,[4] for example, found a lower incidence of HLA-DRw52 in 25 mainland Chinese patients with Vogt-Koyanagi-Harada syndrome than in a normal, ethnoregionally similar control group. These findings are in contrast to the findings in our population. Genotypic analysis of various ethnoregionally distinct populations may define the role of the HLA system in Vogt-Koyanagi-Harada syndrome more precisely.

Two other HLA haplotypes were found to have a higher than expected prevalence in our Cherokee descendant Vogt-Koyanagi-Harada patient population: HLA-A28 and -DR3. Three of the four black patients tested had the HLA-A28 haplotype, whereas none of the white patients had this haplotype. The normal prevalence of HLA-A28 in the black population is estimated to be 18.8%,[21] suggesting that linkage disequilibrium exists between the HLA-A28 haplotype and the Vogt-Koyanagi-Harada syndrome in the descendants of Cherokee Indians.

A similar, weaker association may also exist between the HLA-DR3 haplotype and the Vogt-Koyanagi-Harada syndrome in our population. Three of the seven patients tested, two white and one black, had the HLA-DR3 haplotype. The normal prevalence of HLA-DR3 is estimated to be 21% in the white population and 31.6% in the black population.[22] The possible association of both the HLA-A28 and HLA-DR3 haplotypes with the Vogt-Koyanagi-Harada syndrome in these descendants of Cherokee Indians must be cautiously interpreted, however, because of the small sample size.

In light of the recent evidence that suggests there are specific HLA haplotypes associated with Vogt-Koyanagi-Harada syndrome,[2-5,15] this report may add support to the hypothesis that a gene on, or closely linked to the HLA-DR locus, is somehow involved in the pathogenesis of this condition. However, it is also possible that the increased incidence of HLA-DRw52 phenotype in this unique subgroup of patients may be unrelated to their Vogt-Koyanagi-Harada syndrome. The small number of ethnoregionally homogeneous American Indian descendants with this disorder, coupled with the limited known polymorphism of the HLA-DR locus, precludes reliable statistical analysis.

Recent investigations of the HLA system, however, have shown more genetic diversity and greater polymorphism than previously suspected. Specifically, several new molecular subtypes for many of the HLA antigens, including HLA-DRw52, have been defined. Genetic linkage analysis incorporating the new HLA-DRw52 molecular subtype information may better define, in a statistically significant manner, the precise HLA association of Vogt-Koyanagi-Harada syndrome in descendants of American Indians. The consistent findings of the HLA-DRw52 haplotype in all of the patients assayed in this study, coupled with the frequent occurrence of HLA-DRw52 homozygosity, adds to the increasing evidence that a class II HLA antigen at a D-related locus may predispose to the development of Vogt-Koyanagi-Harada syndrome.

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Conjunctival Involvement in Paraneoplastic Pemphigus

Stephanie J. Meyers, M.D., Gary A. Varley, M.D., David M. Meisler, M.D., Charles Camisa, M.D., and Arden H. Wander, M.D.

Paraneoplastic pemphigus is a recently described autoimmune inflammatory mucocutaneous disease associated with an underlying neoplasm. Although histopathologic and direct immunofluorescence findings of involved skin and mucous membranes are consistent with pemphigus vulgaris, indirect immunofluorescence and immunoprecipitation study results are unique. We treated two patients with non-Hodgkin's lymphoma and paraneoplastic pemphigus. Both patients had bilateral bulbar conjunctival hyperemia and diffuse papillary tarsal conjunctival reactions. One patient had sloughing of conjunctival epithelium and the other had tarsal conjunctival cicatrization and forniceal shortening. Histopathologic findings of conjunctivae obtained from both patients were consistent with pemphigus vulgaris. Diffuse deposition of IgG and C3 in the intercellular substance of the conjunctival epithelium was demonstrated by direct immunofluorescence. Indirect immunofluorescence testing disclosed binding of autoantibodies to rodent bladder and intestinal epithelium. Immunoprecipitation disclosed antibodies reactive to Desmoplakin I (250 kd), bullous pemphigoid (230 kd), Desmoplakin II (210 kd) and 190-kd proteins. Ophthalmologists and pathologists should be aware of the conjunctival changes in paraneoplastic pemphigus.

In 1990, Anhalt and associates[1] described five patients with paraneoplastic pemphigus, an autoimmune mucocutaneous disease associated with underlying neoplasia that clinically and immunopathologically is distinct from other forms of pemphigus. The condition in all patients was characterized by painful mucosal erosions and polymorphous skin eruptions. Three of the patients had conjunctivitis. Two additional cases of paraneoplastic pemphigus with associated conjunctival involvement were subsequently reported.[2,3] Conjunctival histopathologic correlation was lacking in all these cases. Recently, conjunctivitis was reported in a patient with pemphigus associated with bronchogenic cancer.[4] Histopathologic and immunopathologic findings of the conjunctiva were consistent with those found in paraneoplastic pemphigus-involved skin and oral mucosa. However, not all of the criteria to establish a diagnosis of paraneoplastic pemphigus as proposed by Anhalt and associates[1] were fulfilled.

We studied the clinical, histopathologic, and immunopathologic findings of conjunctival involvement in two patients with lymphoproliferative (B-cell) neoplasia who fulfill all criteria for paraneoplastic pemphigus.

Case Reports

Case 1

A 69-year-old man had a two-week history of blistering lesions of the mouth, penis, umbilicus, and hyperemic congested conjunctiva. He had non-Hodgkin's lymphoma, which had been previously treated with chemotherapy. Physical examination disclosed bilateral cervical, supraclavicular, preauricular, axillary, and inguinal lymphadenopathy. He had a marked erosive stomatitis with buccal mucosal and lip involvement and an erosive balanitis with swollen glans penis. Visual acuity was 20/25 in each eye. The eyelids were mildly edematous. There was marked hyperemia and sloughing of the epithelium of the bulbar and palpebral conjunctiva. A diffuse papillary reaction of the palpebral conjunctiva was also observed. Re-

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From the Departments of Ophthalmology (Drs. Meyers, Varley, and Meisler) and Dermatology (Dr. Camisa), Cleveland Clinic Foundation, Cleveland, Ohio; and the Department of Ophthalmology (Dr. Wander), University of Cincinnati, Cincinnati, Ohio.

Reprint requests to Gary A. Varley, M.D., Department of Ophthalmology, Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH 44195-5024.

sults of the remainder of his ocular examination, except for mild cataract changes, were normal. Conjunctival cultures were negative for virus and grew only coagulase-negative staphylococcal species. Histopathologic studies of a skin lesion and bulbar conjunctival biopsies showed suprabasilar acantholysis (Fig. 1). Direct immunofluorescent studies of the skin, foreskin, and conjunctiva showed deposition of IgG and C3c in the intercellular substance of the epidermis. Indirect immunofluorescence testing of the patient's serum with rodent bladder showed intercellular staining. The patient's serum immunoprecipitated a complex of four polypeptides with molecular weights of 250, 230, 210, and 190 kd.

The patient's eyes were treated with topical corticosteroid drops before the initiation of systemic immunosuppression, and the conjunctivitis improved. The patient continued to have sloughing of the skin on his face, nose, arms, hands, and soles. Chemotherapy consisting of vincristine, cyclophosphamide, and prednisone was started. The skin lesions began to reepithelialize over a two-month period. The oral mucosal lesions appeared to respond poorly to systemic immunosuppressive therapy. One month later, the patient became septic, developed respiratory and cardiac failure, and died.

Case 2

A 58-year-old woman had a nonpruritic, erythematous skin rash on her chest, buccal mucosal ulcerations, and cervical, supraclavicular and submental adenopathy. Biopsy of a right cervical lymph node and bone marrow biopsy disclosed a diffuse, small, cleaved-cell lymphoma. She was treated with cyclophosphamide, vincristine, and prednisone. Her cervical and supraclavicular adenopathy resolved and the skin rash improved. However, her mouth lesions persisted despite two more cycles of chemotherapy. Biopsy studies of the mouth lesions disclosed nonspecific inflammation. Four months later the patient's skin rash recurred and the mouth lesions remained. She also had bilateral conjunctivitis associated with a yellowish discharge. Antibiotic drops were started but the patient showed no subjective or objective improvement. Bacterial and fungal conjunctival cultures were negative. Biopsy studies of the skin rash disclosed lichenoid dermatitis. Treatment with dermatologic triamcinolone ointment was begun.

Ophthalmic examination disclosed a best-corrected visual acuity of 20/40 in each eye. There was bilateral upper and lower eyelid erythema. Slit-lamp examination disclosed crusted material along the lashes, conjunctival hyperemia, and thickened tissue along the upper tarsal border. Marked forniceal shortening in both eyes was noted. Mucinous precipitate was observed in the tear film. Biopsy specimens were taken from the midchest, oral mucosa, and bulbar conjunctiva. A regimen of eyelid scrubs, bacitracin ointment, and fluorometholone drops was begun. Oral cyclosporine was also started to treat her skin and mouth lesions. Histopathologic examination of conjunctival biopsied tissue showed suprabasilar acantholysis. Immunofluorescent studies showed deposition of IgG, C3c, and C1q in the intercellular space of the conjunctival epithelium (Fig. 2). Histopathologic studies of the midchest skin biopsy dis-

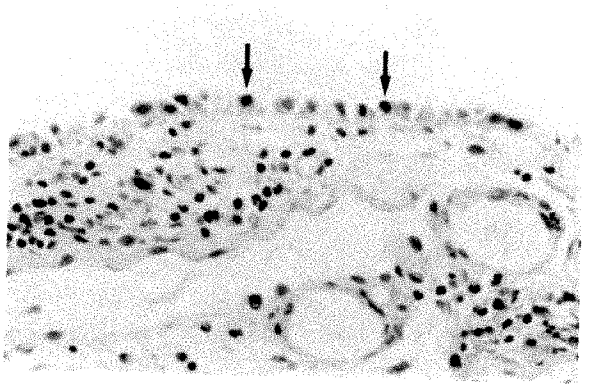


Fig. 1 (Meyers and associates). Case 1. Photomicrograph of bulbar conjunctiva biopsy specimen with suprabasilar acantholysis showing remaining adherent basal epithelial cells (arrows) (hematoxylin and eosin, × 318).

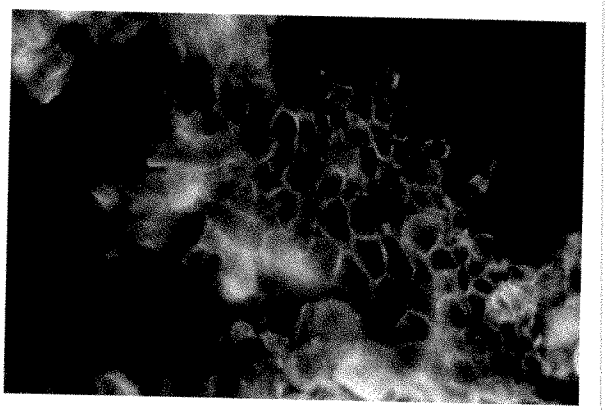


Fig. 2 (Meyers and associates). Case 2. Direct immunofluorescence of conjunctival biopsy specimen demonstrating diffuse deposition of IgG in the intercellular spaces (× 400).



Fig. 3 (Meyers and associates). Case 2. Slit-lamp photograph demonstrating conjunctival scarring with forniceal shortening and symblepharon formation in the right eye.

closed a chronic lichenoid dermal infiltrate. Deposition of IgG, IgA, IgM, and C1q were found in the papillary dermis. Studies of a buccal mucosal biopsy specimen disclosed severe erosive stomatitis. Serum pemphigus antibody titer was positive at 1:320 on monkey esophagus substrate. Serum also reacted to rodent bladder and gastrointestinal epithelium. Immunoprecipitation showed antibodies reactive to 250, and 230, 210, and 190 kd.

Four weeks later, the skin lesions had resolved. However, the severe erosive stomatitis persisted and oral prednisone and azathioprine were instituted. The stomatitis improved but did not completely resolve. The patient's ocular condition progressed to include bilaterally thickened eyelid margins, conjunctival scarring with forniceal shortening, and symblepharon formation (Fig. 3).

Discussion

Both patients described in this study fulfill all criteria as proposed by Anhalt and associates[1] to establish the diagnosis of paraneoplastic pemphigus. These criteria include the following: (1) mucosal erosions and polymorphous skin eruptions with progressive blistering affecting the trunk, palms, and soles in the setting of neoplasia; (2) intraepithelial acantholysis, keratinocytic necrosis, and vacuolar interface dermatitis; (3) direct immunofluorescence testing demonstrating IgG and complement deposition intercellularly as well as granular-linear deposition on the epidermal basement membrane zone; (4) serum antibodies that bind simple, columnar, and transitional epithelium; and (5) immunoprecipitation of antibodies reactive to Desmoplakin I (250 kd), bullous pemphigoid (230 kd), Desmoplakin II (210 kd), and 190-kd proteins.

Conjunctival involvement is an important clinical finding in the spectrum of this disease. The conjunctival inflammation that occurred in our patients was characterized by bilateral bulbar conjunctival hyperemia and diffuse papillary tarsal conjunctival reaction. In Case 1, the patient sloughed his epithelium. This probably represents an acute phase of the disease and may correspond to the pseudomembranous conjunctivitis described by Anhalt and associates.[1] Chronic conjunctival inflammation may lead to cicatrization similar to that found in ocular cicatricial pemphigoid. Lam and associates[4] described cicatrizing conjunctivitis occurring in a patient with skin eruptions, bronchogenic cancer, and acanthosis nigricans with pachydermatoglyphy. While four criteria to establish the diagnosis of paraneoplastic pemphigus were fulfilled, serum antibody immunoprecipitation studies to fulfill the fifth criterion were not done. In Case 2 of our study, the patient who had chronic conjunctivitis subsequently was noted to have superior and inferior forniceal shortening and symblepharon formation. There was a prominent fibrotic band coursing along the superior border of the upper tarsus in both eyes. The conjunctival inflammation observed in Case 2 is similar to the first three clinical stages of ocular cicatricial pemphigoid as described by Foster, Wilson, and Ekins.[5]

The same histopathologic and immunopathologic features found in the skin appear to be found in the conjunctiva as well. Lam and associates[4] observed histopathologic and immunopathologic findings consistent with pemphigus vulgaris in the skin and conjunctiva of their patient. In our report, studies of conjunctiva biopsy specimens also demonstrated histopathologic findings consistent with pemphigus vulgaris, which included suprabasilar acantholysis and mononuclear infiltrates.[6,7] Immunopathologic findings of diffuse deposition of IgG and C3 in the intercellular substance of the conjunctival epithelium consistent with pemphigus vulgaris were also found.[6,7] Obtaining conjunctival tissue for histopathologic and immunopathologic studies may indeed be pivotal in establishing the diagnosis of paraneoplastic pemphigus. This was evidenced by Case 2 in

which the histopathologic findings of cutaneous and buccal mucosal biopsy specimens were misleadingly compatible with lichen planus, and only the biopsy specimens of bulbar conjunctiva disclosed suprabasilar acantholysis consistent with pemphigus. The immunopathologic findings confirmed the diagnosis of paraneoplastic pemphigus.

In all cases of paraneoplastic pemphigus described, including ours, treatment has been directed toward the underlying neoplastic disease with systemic chemotherapeutic and immunosuppressive agents including prednisone.[1-4] Associated skin and mucosal lesions have had a variable response to this therapy. The skin and mucosal changes in our patients seemed to heal with treatment.

Treatment for conjunctival involvement of paraneoplastic pemphigus is uncertain. The patient described by Fullerton and associates[2] failed to show resolution of conjunctival lesions after treatment with oral methylprednisolone, topical corticosteroids, bland emollients, and antifungals. Lam and associates[4] reported persistence of conjunctival hyperemia and mucous discharge with progression to cicatrization despite treatment with oral prednisone and azathioprine and topical antibiotics, artificial tears, and 10% N-acetylcysteine. In our cases, acute conjunctival inflammation responded to systemic and topical therapy and seemed to respond before the resolution of skin and other mucosal lesions, which suggests that topical corticosteroids may have helped reduce the conjunctival inflammation.

Our two cases affirm the involvement of conjunctiva in the paraneoplastic pemphigus syndrome. Further, it is important to realize that conjunctival biopsy specimens may establish the diagnosis when skin and other mucosal biopsy studies fail to do so.

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Optic Neuropathy in Hodgkin's Disease

R. Michael Siatkowski, M.D., Byron L. Lam, M.D., Norman J. Schatz, M.D., Joel S. Glaser, M.D., Sandra F. Byrne, and J. Randall Hughes, B.S.

Hodgkin's disease is a rare cause of infiltrative optic neuropathy, which typically evolves late in the disease course. We managed an unusual case of isolated optic neuropathy in a 21-year-old man occurring during clinical remission from Hodgkin's disease. Radiotherapy and treatment with high-dose systemic corticosteroids resulted in dramatic improvement in vision. Even without other evidence of recurrent disease, acute-onset optic neuropathy in a patient with a history of a lymphoproliferative disorder should raise the question of a reemergence of the malignancy.

CENTRAL NERVOUS SYSTEM involvement in Hodgkin's disease may occur in up to 15% of cases,[1] but optic nerve infiltration is rare. Two histopathologically documented cases have been described.[2,3] More recently, a survey at the Massachusetts Eye and Ear Institute and the Massachusetts General Hospital identified without details only three cases over a 25-year period.[4]

Hodgkin's disease of the central nervous system may rarely be primary,[5-7] but usually is a result of hematogenous metastasis or direct tumor extension from contiguous structures, for example, the retroperitoneal space or paranasal sinuses. Optic neuropathy occurs typically late in the disease course, preceded by other central nervous system or systemic abnormalities. Our case of infiltrative optic neuropathy in Hodgkin's disease documents that this complication may occur as the sole manifestation of disease recurrence in a patient otherwise in clinical remission.

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From the Bascom Palmer Eye Institute, Miami, Florida. This study was presented in part at the 24th Annual Frank B. Walsh Meeting, Los Angeles, California, Feb. 28, 1992.

Reprint requests to Joel S. Glaser, M.D., 900 N.W. 17th St., Miami, FL 33136.

Case Report

A 21-year-old man was initially examined in October 1988 because of complaints of fever, and neck and inguinal masses. Pathologic diagnosis was nodular sclerosis Hodgkin's disease, stage IIIB (disease above and below the diaphragm, and systemic symptoms). Twelve cycles of chemotherapy were prescribed for the patient, but he received only five because of adverse effects (one course of methotrexate, vincristine sulfate, procarbazine, and prednisone; three courses of doxorubicin hydrochloride, bleomycin, vincristine, and dacarbazine; and one course of bleomycin, vincristine, cyclophosphamide, procarbazine, and prednisone). No chemotherapy was received after May 1989 and the patient remained without symptoms for more than two years.

On Aug. 11, 1991, the patient was examined at our institution for loss of vision in the left eye two weeks previously, which was associated with severe orbital pain made worse with ocular movement. The patient also complained of a mild frontal headache and bilateral paresthesias of the chest that extended down both anterior axillary lines.

Neuro-ophthalmic examination disclosed a visual acuity of 20/20 in the right eye, with a full visual field, and normal anterior segment and fundus. The visual acuity in the left eye was counting fingers, with a large central scotoma and an afferent pupillary defect that measured 3.0 log units. The anterior segment was normal and there was no vitreitis. The left optic disk was diffusely swollen with surrounding hemorrhages (Fig. 1). Ocular motility was normal.

B-scan echography showed a normal right optic nerve and a notably enlarged left optic nerve with marked disk elevation (Fig. 2). By standardized A-scan echography, the right optic nerve measured 3.8 mm with a positive 30-degree test (3.2 mm), which indicated increased subarachnoid fluid around the nerve.[8] The left optic nerve was markedly en-

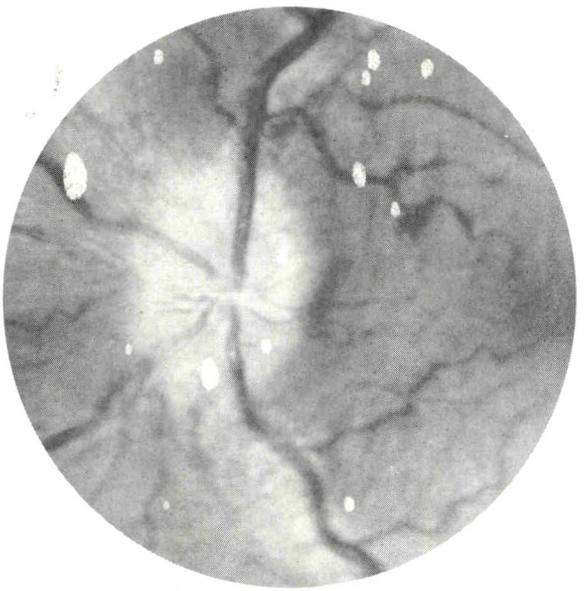


Fig. 1 (Siatkowski and associates). Swollen left optic disk, and peripapillary retinal folds and hemorrhages.

larged with low reflectivity. Its diameter was 6.3 mm with a negative 30-degree test (6.4 mm), which suggested solid thickening of the nerve (Fig. 3). (Normal A-scan values of optic nerve diameter range from 2.3 to 3.3 mm.[8]) Magnetic resonance imaging demonstrated enlargement and gadolinium enhancement of the left optic nerve from the globe to the optic canal (Fig. 4). The right optic nerve was normal.

Results of a general physical examination were normal, without adenopathy or visceromegaly. Lumbar puncture disclosed an opening pressure of 200 mm H_2O, a protein concentration of 40 mg/dl, a glucose level of 65 mg/dl, and no cells. Cerebrospinal fluid VDRL, cryptococcal antigen, and bacterial and fungal cultures were negative. Cytology screen, including immunoassay, detected no malignant cells. Further examination included thoracic radiography, computed tomography of the abdomen and pelvis, and bone marrow biopsy, all of which had normal results.

Lymphomatous infiltration of the left optic nerve was strongly suspected, and 2,000 cGy of radiation were delivered over ten daily sessions to the left optic nerve. Intravenous methylprednisolone, 250 mg four times daily, was administered simultaneously for three days, followed by oral prednisone, 60 mg daily, which was tapered over a three-week period.

Within one week, the visual acuity in the left

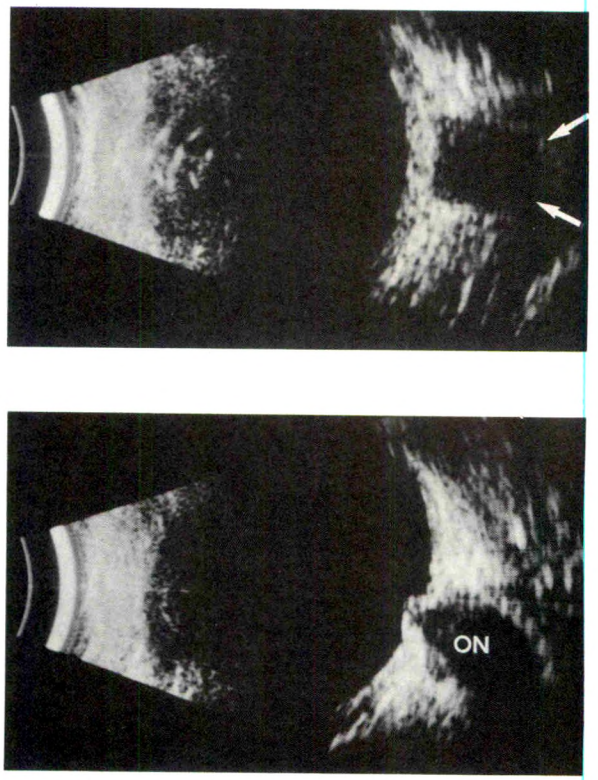


Fig. 2 (Siatkowski and associates). B-scan echograms of left optic nerve. Top, Vertical cross section; arrows indicate enlarged nerve sheath. Bottom, Longitudinal section through elevated disk and anterior optic nerve (ON).

eye improved to 20/400, with a decrease in the size of the scotoma. A six-week follow-up examination on Sept. 25, 1991, disclosed a visual acuity of 20/60 in the left eye. The disk swelling had resolved, but with a trace of temporal pallor. The left afferent pupillary defect now measured 0.9 log unit. Repeat magnetic resonance imaging six weeks after treatment showed a left optic nerve of normal size with only minimal gadolinium enhancement (Fig. 4).

Eight weeks after the visual symptoms developed, a 1.5-cm right anterior cervical lymph node appeared. A biopsy confirmed nodular sclerosis Hodgkin's disease (Fig. 5), and chemotherapy was reinstituted.

Discussion

Hodgkin's disease causes a variety of ophthalmic problems, including oculomotor palsies, proptosis, iritis, retinal arterial and

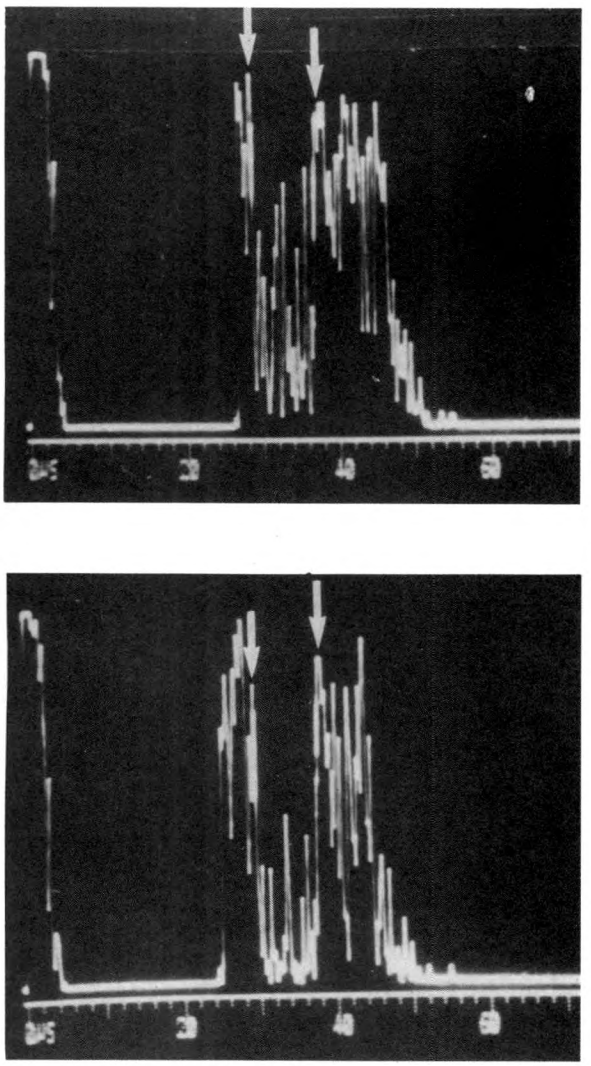


Fig. 3 (Siatkowski and associates). Standardized A-scan echograms of left optic nerve. Top, Primary gaze; arrows indicate optic nerve sheaths (6.3 mm). Bottom, Globe 30 degrees abducted; no change in nerve diameter (6.4 mm).

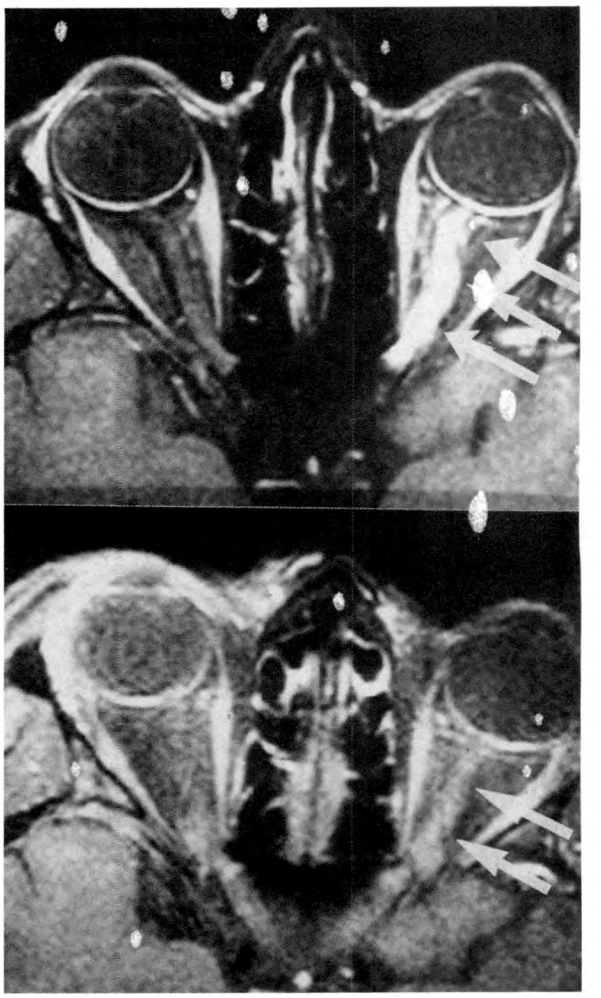


Fig. 4 (Siatkowski and associates). Top, Magnetic resonance imaging, axial view, fat-suppressed, shows marked gadolinium enhancement of left optic nerve (arrows). Bottom, Repeat scan six weeks after treatment. Note marked decrease in gadolinium enhancement of left optic nerve (arrows).

venous occlusions, retinal vasculitis, and Horner's syndrome.[9] Spinal cord compression is the most common expression of central nervous system involvement in Hodgkin's disease and has been well documented.[10-12] Intracranial involvement was described by Murchison[13] in 1870, and since then several other cases have been described.[1,14-17] These cases document involvement of the cerebral cortex, cerebellum, and various cranial nerves.

Optic nerve infiltration occurs in various types of lymphoreticular malignancies, having been found in reticulum cell sarcoma, multiple myeloma, lymphomatoid granulomatosis, and eosinophilic granuloma.[18] The frequency of optic nerve involvement in leukemia ranges from 2% to 33%.[19,20] In non-Hodgkin's lymphomas, although central nervous system involvement occurs in up to 29% of cases,[21] optic neuropathy has been infrequently described.[22-24]

An early case of optic nerve involvement from Hodgkin's disease[2] manifested late in the disease and in the presence of widespread meningoencephalopathy with other clinical and laboratory abnormalities. Optic neuropathy as the initial manifestation of Hodgkin's disease is rare, but was described by Miller and Iliff,[3] who found no other clinical abnormalities except for mild eosinophilia.

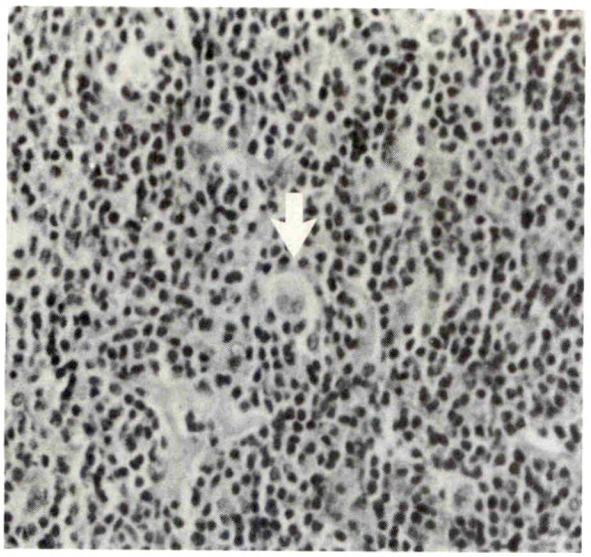


Fig. 5 (Siatkowski and associates). Biopsy specimen of cervical lymph node shows diffuse lymphoid infiltrate with a few eosinophils and polymorphonuclear cells; arrow indicates lacunar cell, a variant of Reed-Sternberg cell seen in nodular sclerosis Hodgkin's disease (hematoxylin and eosin, × 40).

Litvak, Leder, and Kauvar[2] and Miller and Iliff[3] showed that the optic neuropathy in Hodgkin's disease results from direct invasion of the nerve (and in their cases, the chiasm as well) by lymphoma cells, rather than from demyelination. Thus, radiotherapy is the treatment of choice, with systemic corticosteroids having a secondary role. Coppeto, Monteiro, and Cannarozzi[25] described a secondary demyelinative optic neuritis from paranasal sinus lymphoma. The optic nerves appeared normal on computed tomography, and vision improved after treatment with intravenous corticosteroids, with no further recurrences.

In over 95% of cases, central nervous system involvement in the lymphomas occurs with uncontrolled systemic relapse,[26] but optic neuropathy as the sole manifestation of disease recurrence is rare. Kay[24] described such a case in non-Hodgkin's lymphoma, but with many malignant cells in the cerebrospinal fluid, which indicated more diffuse lymphomatous meningitis.

In our case, the two main diagnostic considerations were infiltrative optic neuropathy of lymphomatous origin; or a granulomatous or fungal infectious process, secondary to immunosuppression. Because systemic recurrence of Hodgkin's disease was not evident, the initial chemotherapy may have incompletely penetrated the blood-brain barrier, with the optic neuropathy resulting from residual cells in the central nervous system that escaped the original chemotherapeutic course. The presence of axillary line paresthesias suggested lymphomatous infiltration of thoracic meninges.

Although investigation for recurrence of malignancy was noncontributory in our case, the solid thickening of the optic nerve, with no evidence of infection or cerebrospinal fluid abnormalities, most likely represented recurrence of lymphoma. Diagnostic optic nerve biopsy was briefly considered, but the rapid response to radiotherapy and the subsequent histologically documented disease recurrence confirmed the clinical impression of lymphomatous optic neuropathy.

Our case is important from several standpoints. First, optic neuropathy in Hodgkin's disease is not recognized as an initial sign of disease recurrence. Second, when infiltrative optic neuropathy occurs in the lymphoproliferative disorders, it is usually late in the disease course and is accompanied by other clinical signs and symptoms, as well as abnormal cerebrospinal fluid and pathologic bone marrow. Third, our case demonstrates the value of standardized echography in the assessment of optic nerve diseases.

In patients with a history of lymphoreticular malignancy and acute-onset optic neuropathy, magnetic resonance imaging and orbital echography should be performed promptly. Solid thickening of the optic nerve echographically and marked gadolinium enhancement on neuroimaging indicates lymphomatous infiltration. The absence of other clinical and laboratory abnormalities, including the cerebrospinal fluid, are not inconsistent with this diagnosis, and prompt institution of radiotherapy and systemic corticosteroids may result in a rapid and dramatic improvement of visual function.

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EDITORIAL

Divergent Approaches to the Management of Corneal Ulcers

Jay S. Pepose and Kirk R. Wilhelmus

Elsewhere in this issue, McDonnell and associates reviewed the treatment of corneal ulcers by general ophthalmologists practicing in Southern California. Published recommendations by corneal and external disease specialists state that evaluation of infectious keratitis should include corneal scrapings for smears and cultures.[1-5] Initial treatment with specific or broad-spectrum antimicrobial agents can then be readjusted according to clinical response and laboratory results. Nevertheless, the authors found that many ophthalmologists who were surveyed did not adhere to this practice guideline.

See also p. 531.

The use of the nonspecific term corneal ulcer, may have led some respondents to include both noninfectious and infectious keratitis cases. Recently, Stein and associates[6] identified specific ocular findings that may help differentiate infected from sterile contact lens–related corneal ulcerations. Since the first clear descriptions of suppurative keratitis in the early 19th century, ophthalmologists have searched for appropriate terminology for this condition. The term central corneal ulcer, or more simply corneal ulcer, means corneal infection to most ophthalmologists, although more precise terms such as microbial keratitis are gaining acceptance.

In the study by McDonnell and associates, most responding ophthalmologists estimated that they managed one corneal ulcer case per month. Inasmuch as there may be as many as 30,000 cases of microbial keratitis per year in the United States, any one of the 11,600 ophthalmologists currently in practice would be expected to manage not more than an average of five cases annually. It is difficult to determine whether terminology, overdiagnosis, differences in the underlying population, or an unrepresentative sample accounts for this discrepancy between expected and respondent estimates. Because only 62 ophthalmologists from two California counties responded to the survey, inferences drawn from the study about national practice patterns may be problematic.

Despite these methodologic shortcomings, the study suggested that nearly 50% of all patients (274 of 560 patients) in this community in whom a corneal ulcer was diagnosed were treated without a microbial culture having been obtained; and that more than 80% of the responding ophthalmologists (55 of 64 respondents) prescribed nonfortified, commercial-strength antibiotics for the initial management of corneal ulcers. Furthermore, 6% of the survey respondents (six of 64 respondents) used a topical corticosteroid as part of their routine initial therapy. This is a striking result, given the extensive experimental data that indicate the potential exacerbation of corneal infection by topical corticosteroids when used alone early in treatment or before adequate antimicrobial therapy is implemented.[7,8]

The study focuses on several important questions regarding the management and delivery of ophthalmic care. What accounts for these prevalent deviations from recommended practice? Does the preferred practice guideline ensure the best clinical outcome? Is this true for all patients or are there specific clinical signs, such as central ulcers, that are more likely associated with an adverse outcome? When analyzed by a cost-benefit ratio, is there disparity between the cost inherent to the preferred practice pattern vs the costs of an adverse outcome weighted by the probability of its occurrence?

To explain the variance with recommended practice, perhaps some ophthalmologists have not received adequate instruction in the optimal care of microbial keratitis. Despite the better recovery of responsible microorganisms by direct inoculation of corneal material onto culture media, some training programs permit or encourage the use of a transport tube or do not designate a procedure for residents to follow. Ophthalmologists who have been in practice while these concepts have evolved may not be aware of current recommendations. If current preferred practice guidelines are not well known, ophthalmology teaching programs must strengthen their continuing education efforts. More likely, ophthalmologists in community practice have grappled with the need, accessi-

bility, and costs of laboratory testing for suspected bacterial keratitis and have decided that it might not be appropriate for all patients. A rough cost-benefit analysis based on individual practice experiences probably accounts for the finding that three of four ophthalmologists surveyed believed that cultures were not necessary in the management of all corneal ulcers. Broad-spectrum agents such as cephalosporins, aminoglycosides, and, more recently, fluoroquinolones[9] are effective in treating most patients. In the study by McDonnell and associates, only 6% of patients with corneal ulcers (35 of 560 patients) were referred to corneal specialists because of worsening or failure to improve. Unfortunately, factors other than antibiotic selection also determine clinical outcome.[7,10] For microbial keratitis, most ophthalmologists do not examine a sufficient number of patients to assess adequately the incidence or impact of an adverse outcome resulting from their particular management.

Although McDonnell and associates raise many important issues concerning the community care of corneal ulcers, it is beyond the stated scope of their study to provide a true cost-benefit analysis. An accurate cost-benefit analysis must consider not only the likelihood, but also the morbidity associated with an adverse outcome. For example, community fitting of extended-wear contact lenses[11-14] has been associated with corneal ulcer rates as high as 2% to 7%, with cumulative estimates of 8,000 to 10,000 corneal ulcers annually.[15] Although the incidence of ulceration per year of contact-lens use is extraordinarily low,[16] this must be weighed against the potential of permanent visual loss in otherwise normal eyes.

More information is needed about the general care and evaluation of corneal ulcers to determine how many patients without corneal cultures have vision-limiting corneal scarring, require penetrating keratoplasty, or incur substantial financial loss in the form of medical bills or time lost from work. What is the overall effect on quality of life in these patients? Patients may not respond to treatment because of resistant bacterial or fungal keratitis, amebic keratitis, and various nonmicrobial causes of corneal ulceration. Can we compare the cost or inconvenience of obtaining laboratory tests with the functional impact of resulting corneal disease in this subgroup of patients? General ophthalmologists and corneal specialists must collaborate to assess how empiric treatment without microbial assessment affects clinical outcome and subsequent quality-of-life issues. A sophisticated cost-benefit analysis would consider a broad base of patients and practices, allowing the cost-benefit result to vary by patient characteristics and initial clinical signs.

Attention is being directed to cost-benefit analysis, outcome studies, and practice guidelines in the 1990s as third-party payers struggle in their effort to contain health care costs. Should the standard of care in the community dictate appropriateness or should expert opinions on optimal evaluation be the defining standard? McDonnell and associates highlight an important issue in quality assurance that should be critically explored to determine how to reconcile the divergence in prevailing vs recommended modes of treatment.

Reprint requests to Jay S. Pepose, M.D., Department of Ophthalmology and Visual Sciences, Box 8096, Washington University School of Medicine, 660 S. Euclid Ave., St. Louis, MO 63110.

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LETTERS TO THE JOURNAL

Ultrastructure of Human Immunodeficiency Virus in Corneal Epithelial Scraping

Bruce L. Johnson, M.D., and Andrew E. Holzman, M.D.

Departments of Pathology (B.L.J.) and Ophthalmology (A.E.H.), University of Pittsburgh School of Medicine and the Eye Pathology Laboratory, Eye and Ear Institute, Montefiore University Hospital.

Inquiries to Bruce L. Johnson, M.D., Eye Pathology Laboratory, Eye and Ear Institute, 203 Lothrop St., Pittsburgh, PA 15213.

Human immunodeficiency virus (HIV) has been identified in tears, cornea, conjunctiva, and retina.[1-3] As a result, corneal donor tissue is routinely screened for HIV antibodies before transplantation. Proper precautions regarding possible contamination of gloves, contact lenses, tonometers, and other instruments by tears or surface-infected cells should be the concern of all ophthalmologists and ophthalmic personnel. We found ultrastructural HIV particles in the corneal epithelium of a patient with acquired immunodeficiency syndrome (AIDS).

A 46-year-old man with AIDS who had been treated for multiple opportunistic infections, including pneumocystosis, cryptococcal septicemia, and cytomegalovirus retinitis, had red eyes at initial examination. Examination disclosed a visual acuity of R.E.: 20/40 and L.E.: 20/60. The conjunctiva was injected and chalky-white corneal epithelial and subepithelial snowflake deposits were present bilaterally. Gram and Giemsa staining of corneal scraping smears disclosed intracellular inclusion bodies consistent with microsporidiosis. A scraping fragment from a formalin-fixed smear was lifted from the glass slide and processed for electron microscopy. An unexpected ultrastructural finding was the presence of numerous HIV particles within the corneal epithelial cells (Figs. 1 and 2). These were concentrated in the cytoplasm near the cell borders. They were morphologically similar to the virions described by others in lymphocytes, cornea, and brain tissue from patients with AIDS.[3,4] These virions have a greater variation in size (70 to 160 nm) and more pleomorphism than was originally believed.[4] Variation in size, shape, number, and location of the dense nucleoid within the particle is now recognized. Conical or tapered, less dense cores were seen in many of the particles in our case, but were suboptimally visualized because of poor preservation of the tissue. Recovery and processing of conjunctival epithelial cells via an impression technique for electron microscopy may be a more effective noninvasive and morphologically superior approach to that used in our case.[5]

Although HIV has been demonstrated in conjunctival and corneal epithelial cells by immunofluorescent techniques, only rarely have viral particles been demonstrated ultrastructurally in corneal sections.[3] Meyenhofer and associates[4] emphasized that morphologists should be aware of the variation in appearance of HIV particles when searching for them in tissue. Our findings strengthen the postulate that the cornea is not merely contaminated by virus in the tear film, but may be capable of supporting

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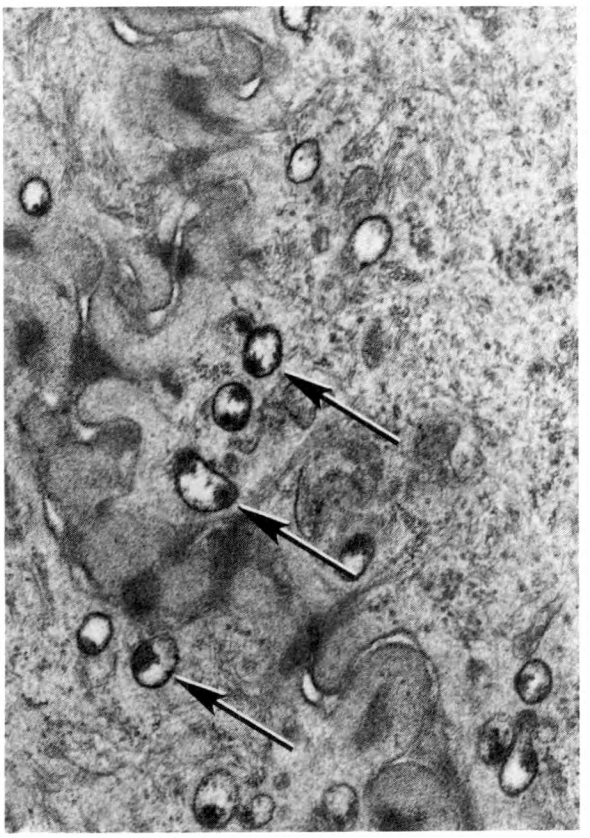


Fig. 1 (Johnson and Holzman). Numerous viral particles (arrows), many of which contain one or two dense nucleoids and often eccentrically placed, are present within the cytoplasm of two epithelial cells adjacent to desmosomes (× 40,000).

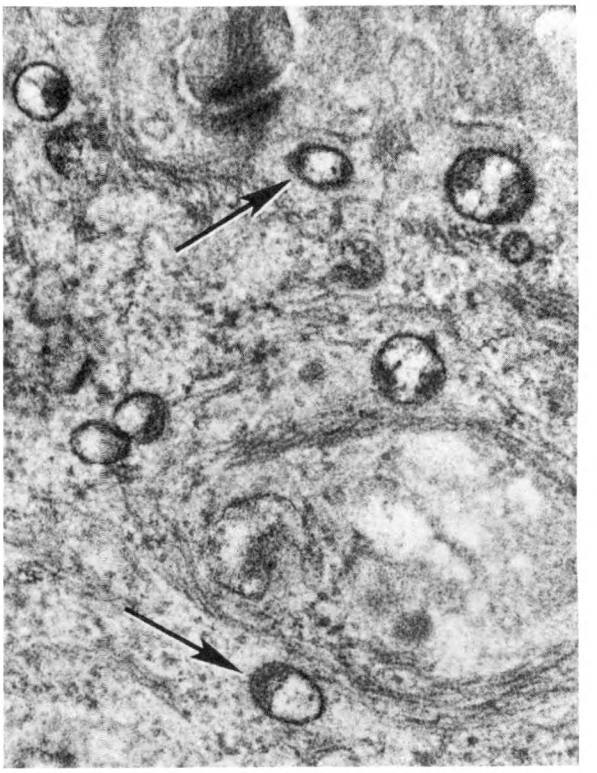


Fig. 2 (Johnson and Holzman). Higher-power view of corneal epithelial cell shows virions with crescentic densities (arrows) along the particle membranes. This is characteristic of immature HIV virions and implies viral replication (× 76,000).

HIV infection. At present, it is unclear if the cornea and conjunctiva are sites of replication of the virus particles, but the presence of immature forms supports this. Although there is currently no documentation of HIV transmission via corneal transplantation, the demonstration of virus particles within corneal epithelium emphasizes the continuing need for vigilant screening of donor corneas.

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Propofol and Surgical Contamination in Strabismus Surgery

Dorothy V. Bautista, M.D., F.R.C.S.(C.), and Ronald V. Keech, M.D.

Department of Ophthalmology, University of Iowa Hospitals and Clinics.

Inquiries to Ronald V. Keech, M.D., Department of Ophthalmology, University of Iowa Hospitals and Clinics, Iowa City, IA 52246.

Propofol (diprivan-ICI) is a short-acting intravenous hypnotic agent used for the induction and maintenance of general anesthesia. Propofol has become popular for outpatient surgery because of the shorter recovery period, compared with that of other general anesthetics.[1,2] We have found propofol to be useful as an anesthetic agent for strabismus surgery, especially when adjustable sutures are used.

Common adverse effects of propofol include hypotension, nausea, and burning at the administration site. A less common adverse effect is hypersalivation. This effect can be potentially detrimental in strabismus surgery because of the close proximity of the operative site to the patient's mouth and nose. Since the introduction of propofol for use in the ambulatory surgical center of our institution, we have noted an increased incidence of oral and nasal secretions in our patients during surgery that, in some cases, has resulted in contamination of the operative field.

A 35-year-old man underwent a re-operation for exotropia. Anesthesia was induced with propofol and fentanyl. Intubation was performed by using atracurium. Maintenance of anesthesia was achieved with nitrous oxide, oxygen, and propofol. The patient was prepared and draped, leaving the eyes exposed. An occlusive plastic drape was placed at the edge of the towel drape to form a seal between the patient's skin and the towels. After approximately one hour of surgery, nasal secretions were seen penetrating the surgical drapes and entering the operative field. The area was immediately irrigated with saline, the drapes removed, and nasal secretions aspirated. Nasal packing was inserted into the nostrils. The surgical site was prepped and draped again and the eye irrigated with an ophthalmic antibiotic solution. At the end of the procedure, an antibiotic ointment was instilled into the conjunctival sac. There were no postoperative complications.

A 5½-year-old boy underwent strabismus surgery for esotropia. Anesthesia was induced with halothane and maintained with propofol, nitrous oxide, and oxygen. Intubation was performed by using atracurium and glycopyrrolate. The patient was prepared and draped, leaving the eyes exposed. An adhesive plastic drape was used to form an occlusive seal between the patient's skin and the towels. Upon completion of the operative procedure, during closure of the conjunctival peritomy of the second operated-on eye, oral and nasal secretions were seen leaking through the drapes and contaminating the operative field. The eye was irrigated with normal saline, and a subconjunctival injection of cefazolin was administered. Antibiotic ointment was instilled into the conjunctival sac of both eyes. There were no postoperative complications.

We have had two additional cases where the cloth drapes adjacent to the operative field were saturated with nasal secretions. In both cases, the drapes were changed before the operative field became contaminated.

The cause of excessive oral and nasal secretions in these cases is unknown. In our experience, this complication appears to be more likely in adult patients undergoing relatively long procedures. We have used anticholinergic agents as well as nasal packing with limited success in reducing secretions. Other anesthetic agents may contribute to the increased secretions. However, we believe propofol is the most likely causative agent. Neither of us has seen this complication when propofol was not used. Propofol is well known to increase secretions, although the mechanism remains unclear. Surgeons who operate near the patient's nose or mouth should be aware of this potential complication.

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Vertical Fusion Amplitude in Normal Adults

Kumudini Sharma, M.D., and Aziz S. Abdul-Rahim, M.D.

Department of Ophthalmology and Visual Sciences, Texas Tech University Health Sciences Center. Supported in part by an unrestricted departmental grant from Research to Prevent Blindness, Inc., New York, New York.

Inquiries to Aziz S. Abdul-Rahim, M.D., 15151 National Ave., Suite 5, Los Gatos, CA 95032.

The normal range of vertical fusion amplitude in clinical practice has been stated to be on the order of 3 to 6 prism diopters.[1] However, we have observed higher values in normal patients on several occasions. In order to define a normal range better, we measured the vertical fusion amplitudes in normal volunteers by using a clinically practical technique.

The following protocol was approved by the Texas Tech University Health Sciences Center Institutional Review Board for the Protection of Human Subjects. Outpatients and staff members of the Department of Ophthalmology and Visual Sciences of Texas Tech University Health Sciences Center were recruited. History of ocular disease or double vision was obtained. Visual acuity testing, cover testing, and ocular ductions were performed on each subject. Those who could not be refracted to 20/20 in each eye were excluded from the study. With spectacle or contact lens correction in place, the subject was asked to fixate upon a projected single 20/40 Snellen letter under ordinary room illumination. Vertical fusion amplitude was measured with a Berens No. B-14 vertical prism bar (R. O. Gulden & Co., Inc., Elkins Park, Pennsylvania). Increasing base-down prism was introduced stepwise before one eye until the subject was subjectively unable to fuse the two images in ten seconds after an increase in prism power. Increasing base-up prism was then introduced before the same eye until the subject was again unable to fuse the two images in ten seconds. These measurements were repeated to insure reliability. All measurements were accomplished in less than three minutes. The vertical fusion amplitude was recorded as the sum of base-down and base-up prism the patient was able to fuse.

Sixty subjects between the ages of 18 and 63 years (median, 33 years) were included. There were 40 women and 20 men. No subject had a history of double vision. Six subjects had exophoria at distance of up to 6 prism diopters. There were no subjects with tropias, esophoria, or hyperphoria.

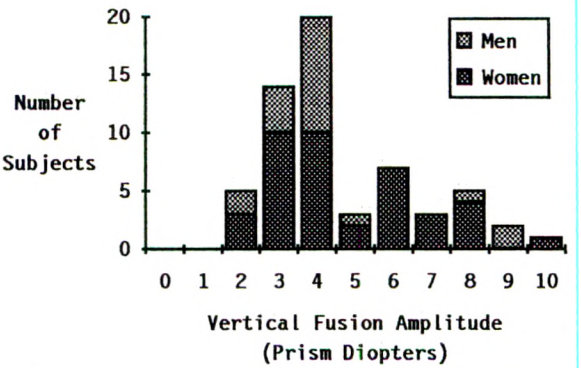


Figure (Sharma and Abdul-Rahim). Vertical fusion amplitudes of 60 adult volunteers.

The mean vertical fusion amplitude was 4.63 prism diopters, with a range of between 2 and 10 prism diopters (Figure). In each subject there was 1 prism diopter or less of variability between repeated measurements. The mean vertical fusion amplitude for women was 4.78; for men it was 4.35 ($P = .44$). The mean vertical fusion amplitude for the six exophoric subjects was 4.00; for the remaining orthophoric subjects the mean was 4.70 ($P = .42$). The P values were obtained by two sample *t*-test with pooled standard deviations, but other approaches yielded closely similar results. No significant difference could be inferred between men and women or between individuals who were exophoric and orthophoric in the general population.

Many technical variables influence the measured vertical fusion amplitude. Higher values are obtained with rotary prisms than with square prisms or prism bars.[2] Using larger targets, slowing the rate of increasing prism power, or adding peripheral retinal to foveal stimuli will increase vertical fusion amplitude, with values up to 16 prism diopters reported in a laboratory setting.[3,4] We chose to use a technique that is rapid, simple, and easily accomplished in a busy outpatient clinic setting. The range of vertical fusion amplitude in our series of normal subjects was 2 to 10 prism diopters, which is somewhat higher than previously reported.[1]

Measurement of vertical fusion amplitude is particularly helpful in the examination of patients with trochlear nerve palsy. The finding of a vertical fusion amplitude of up to 30 prism

diopters in a patient with trochlear nerve palsy strongly suggests that the palsy is congenital, and therefore benign.[5] However, our experience with normal subjects shows vertical fusion amplitude should not be used in support of a diagnosis of congenital trochlear nerve palsy unless it is greater than 10 prism diopters.

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Moraxella Infection of a Scleral Buckle

David Callanan, M.D., and Patrick E. Rubsamen, M.D.

Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami School of Medicine.

Inquiries to Patrick Rubsamen, M.D., Bascom Palmer Eye Institute, P.O. Box 016880, Miami, FL 33101.

Infection and extrusion of silicone explants are potential long-term complications of the scleral buckling procedure. Although infection and extrusion are uncommon, an incidence of 3%[1] to 5%[2] was reported in two large series. Arribas and associates[3] demonstrated the beneficial effect of preoperative soaking of the sponge in antibiotics, which is a common current practice. The most commonly cultured organisms are the gram-positive species such as *Staphylococcus*. However, we treated a woman with scleral-buckle infection caused by *Moraxella catarrhalis*.

A 63-year-old woman underwent successful repair of a retinal detachment in the left eye in 1987, and subsequently underwent an uncomplicated cataract extraction. She had chronic renal failure secondary to polycystic kidney disease and was treated with long-term hemodialysis. She was seen elsewhere in April 1991 because of a three-week history of irritation, redness, and chemosis of the left eye and she was treated with a topical combination of dexamethasone and neomycin for presumed conjunctivitis. She was referred to our institution several days later because of a three-day history of progressive loss in visual acuity and severe pain in the left eye. Visual acuity was R.E.: 20/30 and L.E.: hand motions. The right eye had mild nuclear sclerosis of the lens and myelinated nerve fibers in the fundus. There was severe injection and chemosis of the bulbar conjunctiva, retraction of the conjunctiva superotemporally, and exposure of the encircling element with mucopurulent discharge. The cornea was clear, the anterior chamber had moderate flare without cells or hypopyon, and intraocular pressure was 12 mm Hg in both eyes. A posterior chamber intraocular lens was well positioned and the vitreous had moderate haze and trace cells. An encircling scleral-buckle effect was present. Superotemporally, there was an exudative detachment of the retina with fluid extending into the macula in association with a localized ciliochoroidal detachment. The patient was taken to the operating room and a 3 × 5-mm silicone sponge was removed. There was marked inflammation, but no necrosis of the underlying sclera. Subconjunctival injections of gentamicin and vancomycin were given. The cultures obtained from both the sponge and the conjunctiva at the time of the surgical procedure grew *M. catarrhalis*. The organism was resistant to penicillin and sensitive to ciprofloxacin and gentamicin. She did well postoperatively on a regimen of topical gentamicin only and was discharged. Two weeks postoperatively, she had no discomfort, visual acuity was hand motions, and intraocular pressure was 7 mm Hg. There was less conjunctival injection and trace flare in the anterior chamber. The exudative retinal detachment had almost completely settled without any evidence of unsupported new or old retinal breaks. The

patient was followed up for one month, at which time she developed an unrelated small-bowel infarction and subsequently died.

Infection of a scleral buckle with *Moraxella* species is unusual. The patient had no history or evidence of angular blepharitis, a condition typically associated with ocular *Moraxella* infections. *Moraxella catarrhalis* grows well on either blood or chocolate agar, is typically resistant to penicillin, and is sensitive to aminoglycosides. Our case reinforces the value of cultures in scleral-buckle infections to identify the organism and subsequent treatment with appropriate antibiotics.

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Severe Anaphylactic Reaction After Indocyanine Green Fluorescence Angiography

Sebastian Wolf, Ph.D., Oliver Arend, M.D., Karin Schulte, M.D., and Martin Reim, M.D.

Augenklinik der Med. Fak. der Rheinisch-Westfälischen Technischen Hochschule Aachen.

Inquiries to Dr. Med., Dr.-Ing. S. Wolf, Augenklinik Medizinischen Fakultät der Rheinisch-Westfälischen Technischen Hochschule Aachen, Pauwelsstrasse 30, D-5100 Aachen, Germany.

The development of new imaging technology has led to renewed interest in choroidal angiography with indocyanine green dye (Cardio-Green) for the management of exudative sequelae of age-related maculopathy.[1,2]

A 62-year-old woman with age-related maculopathy complained of decreased vision. The fluorescein angiogram indicated a hidden subretinal neovascular membrane. Choroidal angiography with indocyanine green angiogram was performed one hour after fluorescein angiography. Indocyanine green, 50 mg dissolved in 3 ml of aqueous solvent, was injected into the antecubital vein. Approximately 30 seconds after injection the patient developed generalized pruritus, labored breathing with wheezing, and hypotension. Her blood pressure dropped to 55/40 mm Hg. We administered 0.5 ml of 1/1,000 epinephrine, 250 mg of corticosteroid, 1 ml of theophylline, and 500 ml of hydroxyethyl starch as a plasma-expander by intravenous infusion. Her breathing returned to normal after five minutes and the blood pressure stabilized at 120/70 mm Hg. She was kept for observation in the cardiac care unit for 24 hours and recovered uneventfully. The patient had no medical or family history of atopy. No history of iodine allergy was elicited.

Indocyanine green is a tricarbocyanine organic dye with a molecular weight of 775. The commercial preparation contains a small amount (less than 5%) of iodine for stabilization. Indocyanine green is widely used for the determination of cardiac output and liver function. The advantages of indocyanine green for choroidal angiography are its absorption and fluorescence in the near infrared, and its high binding rate to plasma proteins. These properties allow visualization of subretinal neovascularization, which is undetected by fluorescein angiography.

Nausea and vomiting, sometimes seen with fluorescein angiography, are almost never seen with indocyanine green dye. However, a fatal reaction after indocyanine green administration during cardiac catheterization was reported.[3] This anaphylactic reaction was attributed to the iodine additive. Fatal reactions are reported to occur in 1:10,000 to 1:100,000 procedures after intravenous use of iodine-containing contrast media.[4] This is at least six times higher than the estimated risk for death after fluorescein angiography.[5]

Our case demonstrates that despite careful screening of patients for history of iodine sensitivity, anaphylaxis can occur with the use of indocyanine green choroidal angiography. Therefore, preparations for emergency resuscitative measures must be readily available.

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Intraconjunctival Cavitary Inclusions of Silicone Oil Complicating Retinal Detachment Repair

Sean P. Donahue, M.D., Thomas R. Friberg, M.D., and Bruce L. Johnson, M.D.

Departments of Ophthalmology (S.P.D., T.R.F.) and Pathology (B.L.J.), Eye and Ear Institute, University of Pittsburgh.

Inquiries to S. P. Donahue, M.D., Department of Ophthalmology, 203 Lothrop St., Pittsburgh, PA 15213.

A 34-year-old man residing in a state psychiatric institution had an episode of self-inflicted trauma in which he struck himself about the head. He sustained a large retinal detachment with a superior flap tear and underwent pars plana vitrectomy, pars plana lensectomy, placement of 1,000 cs silicone oil for tamponade, scleral buckle, and endolaser treatment three days after the injury. Over the next 2½ years, he had repeated episodes of self-inflicted trauma and eventually had a posttraumatic giant retinal tear with a foveal detachment. When the conjunctiva was opened in the operating room, multiple subconjunctival deposits of silicone oil were observed 360 degrees around the anterior globe and were not associated with any sclerotomy sites (Fig. 1). All three previous sclerotomy sites were well healed. Under the operating microscope, many episcleral and intrascleral microspherules of oil were present. Although many of these droplets could be washed from the surface of the globe, others remained within the sclera itself and could not be removed. When the silicone oil was replaced during the second surgical procedure, it was apparent that the oil had emulsified considerably, and multiple microscopic spherules had accumulated at the posterior surface of the cornea in this aphakic eye.



Fig. 1 (Donahue, Friberg, and Johnson). Case 1. Macroscopic view of the unfixed conjunctival biopsy specimen that contained numerous various-sized cavities filled with viscid clear material (× 20).

Pathologic examination of the inferior bulbar conjunctiva demonstrated a pink, finely vascularized segment of tissue that was extremely buoyant in the fixative (Fig. 1). It contained multiple minute gray translucent cavities of up to 1 mm in size. Microscopic examination demonstrated clear vacuoles and silicone oil deposits in the substantia propria of the conjunctiva, some of which were lined by multinucleated foreign body-type giant cells (Fig. 2).

Several large-series reviews of silicone oil

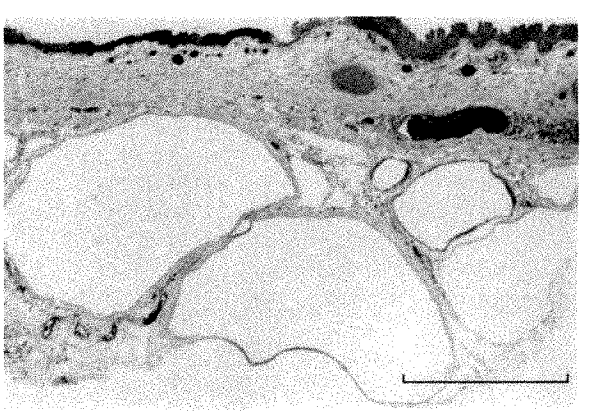


Fig. 2 (Donahue, Friberg, and Johnson). Case 1. Microscopic view of the biopsy specimen in Figure 1. Numerous various-sized clear vacuoles are seen deep within the conjunctival substantia propria (hematoxylin and eosin, × 100). Bar represents 500 μm.

have been published during the past five years. None describes the apparent transscleral migration of emulsified oil.[1-5] Federman and Schubert[3] described subconjunctival deposits of oil in four of 170 eyes (2.4%), but the deposits were thought to be secondary to extravasation of oil through the sclerotomy site and induced symptomatic pain.

Our patient had multiple cavitary inclusions of silicone oil throughout both the conjunctiva and sclera anterior to the equator. The oil could have left the vitreous cavity by several mechanisms. Although extrusion through the sclerotomy is plausible, the sclerotomy sites (as determined by the nylon suture remnants) were completely healed. Local scleromalacia was not evident, as might be seen if trauma-induced increases in intraocular pressure forced oil through healing sclerotomies. Furthermore, there was no increased density of oil droplets near the former sclerotomy sites. A direct transscleral passage of emulsified oil droplets could explain the intrascleral deposits and the diffuseness of the process, and would be more likely to occur in a person with severe myopia with correspondingly thin sclera and whose eyes had increased intraocular pressure associated with repeated trauma. Finally, microscopic oil droplets could have reached the conjunctiva via the trabecular meshwork and the episcleral veins (the normal outflow tract of the eye), particularly because the patient struck his oil-filled eye repeatedly several months after the first operation. The patient was not cooperative enough to examine the angle structures gonioscopically. Because this patient's eye was not removed, the angle structures could not be examined histologically.

On the basis of our clinical examination, coupled with the history of silicone oil emulsification followed by repeated direct ocular trauma, we believe silicone oil can exit from an intact oil-filled eye. Although the complication must certainly be rare, it may lead to conjunctival hyperemia, foreign-body inflammation, and a grossly abnormal appearance of Tenon's capsule and conjunctiva.

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Conjunctival Concretions

Vera O. Kowal, M.D., Anthony P. Adamis, M.D., and Daniel M. Albert, M.D.

Department of Ophthalmology, Massachusetts Eye and Ear Infirmary.

Inquiries to Anthony P. Adamis, M.D., Cornea Service, Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114.

A 19-year-old black, South African woman had a three-year history of intermittent bilateral ocular irritation and foreign-body sensation. She had no other associated symptoms. She denied any history of external eye disease and had never used any eye medications.

Visual acuity was 20/20 in both eyes. The eyes appeared to be white with no signs of active inflammation. Minimal superficial punctate keratitis was noted at the superior aspect of both corneas. Herbert's pits were not present. Numerous yellow-white concretions of varying size were present on the superior palpebral conjunctivae of both eyes (Fig. 1). Some concretions were protruding through the conjunctival epithelium and could easily be dislodged with a 27-gauge needle. Conjunctival scarring was notably absent. Results of the remainder of the ocular examination were normal.

Microbiologic studies of the concretions were negative, and the patient's serum calcium and cholesterol profile was normal. Histologic ex-

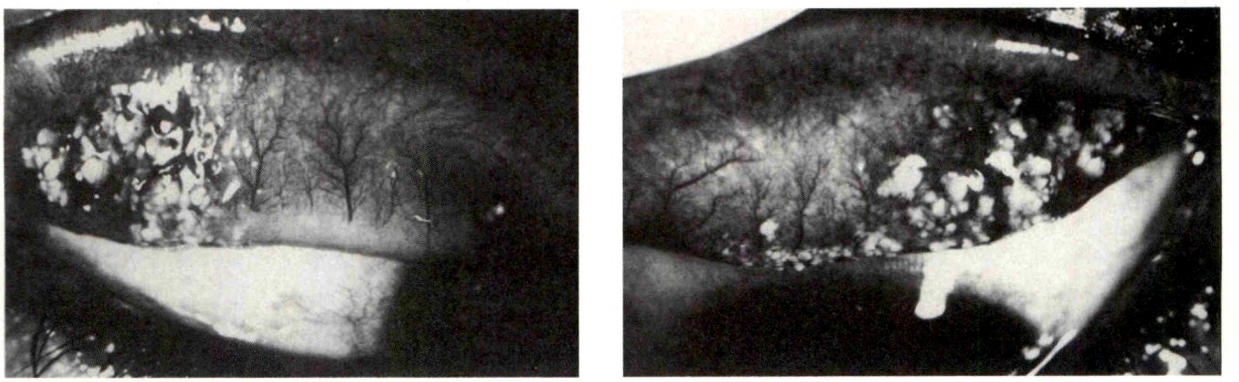


Fig. 1 (Kowal, Adamis, and Albert). Photographs of the right and left everted upper eyelids demonstrate numerous palpebral conjunctival concretions.

amination disclosed the concretions to be composed of eosinophilic, amorphous, hyalinelike material, which stained positively for neutral mucopolysaccharide with periodic acid-Schiff stain (Fig. 2).

A few small, yellow-white asymptomatic conjunctival concretions are often found routinely on examination, typically in the elderly or after chronic conjunctival inflammation.[1] Confluent concretions are much less common, but may cause significant irritation.[2] The term, conjunctival lithiasis, is a misnomer because stains for calcium are routinely negative.[2,3] Calcification does not appear to be an important process in the formation of concretions. Evidence suggests that in chronic inflammatory conditions, concretions are composed of mucinous secretions of transformed conjunctival glands admixed with degenerated epithelial cells.[3]

Superior palpebral conjunctival concretions are often seen in trachoma, and are strongly associated with the presence of Herbert's pits.[4] Concretions were described with the prolonged use of sulfadiazine eyedrops.[5] In that case, various analytical techniques were used to identify recrystallized sulfadiazine as the substance contained in the concretions. The origin of the conjunctival concretions in our patient is unknown. She was young, healthy, and had denied prior ocular disease or the use of eye medications. Despite coming from an area where trachoma is prevalent, she had no evidence of scarring to suggest prior infection.

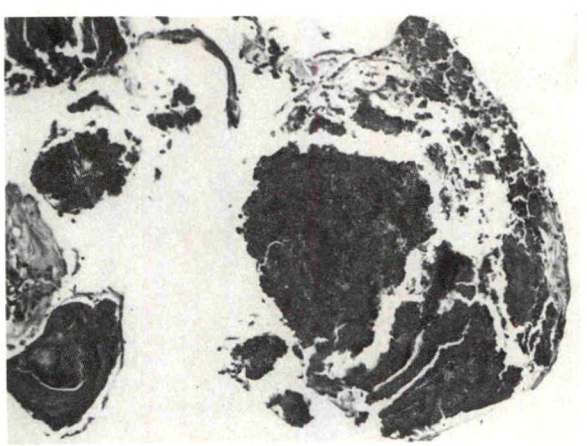


Fig. 2 (Kowal, Adamis, and Albert). Amorphous, eosinophilic histologic appearance of a conjunctival concretion (hematoxylin and eosin, × 40).

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Development of a Retinal Artery Macroaneurysm at the Site of a Previously Detected Retinal Artery Embolus

Robert A. Wiznia, M.D.

Department of Ophthalmology and Visual Science, Yale University School of Medicine.

Inquiries to Robert A. Wiznia, M.D., 850 Howard Ave., New Haven, CT 06519.

Although the origin of acquired retinal artery macroaneurysms is not entirely certain, several conditions associated with focal arterial wall damage have been implicated.[1] Inherent weaknesses, such as arterial bifurcations and arteriovenous crossing sites, as well as general conditions such as arteriosclerosis, aging, and hypertension have been noted in several series.[1,2] Increased serum lipids, branch retinal vein occlusion, branch retinal artery occlusion,[2,3] and diabetes mellitus[3] are other diseases with an increased association.

Emboli are frequently seen near macroaneurysms.[1,3] However, it is rare for an embolus to be noted initially in a retinal artery followed by development of a macroaneurysm at the same location. Arruga and Sanders[4] did not note such an occurrence in a series of 70 patients with retinal embolism. Two such cases have been described, one by Lewis, Norton, and Gass[1] and the other by Khalil and Lorenzetti.[5] I managed an additional case in which an embolus led to the development of a macroaneurysm at the same location in a previously normal cilioretinal artery.

A 77-year-old white man was first examined by me because of age-related macular degeneration on April 22, 1986. Best-corrected visual acuity was R.E.: 20/400 and L.E.: 20/30. He had a hemorrhagic disciform lesion in the right macula and atrophic loss of retinal pigment epithelium in the left macula. Over the next 14 months, the disciform process reached an involuted end stage with a best-corrected visual acuity of 20/200 in the right eye.

His disease course remained stable until he was noted to have a small embolus in the cilioretinal artery, located at the inferonasal edge of the macula of the left eye on Jan. 7, 1991 (Fig. 1). Visual acuity in the left eye was 20/30. Duplex carotid ultrasonography disclosed mild bilateral calcific plaque formation in the common carotid bifurcation and origin of the internal carotid arteries without marked stenosis. On April 15, 1991, the patient noted blurred vision in his left eye, which was found to be caused by retinal hemorrhage associated with a retinal artery macroaneurysm (Fig. 2). Visual acuity was 20/70 in the left eye. By April 30, 1991, additional hemorrhage and edema were noted and visual acuity was 20/400 in the left



Fig. 1 (Wiznia). Fluorescein angiogram delineates an embolus in the cilioretinal artery at the inferonasal edge of the macula in the left eye on Jan. 7, 1991.



Fig. 2 (Wiznia). Retinal artery macroaneurysm is present at the previous site of the embolus as demonstrated in the late venous-phase angiogram obtained on April 15, 1991.

eye. The patient would not consent to laser treatment at any time during his treatment course. Unfortunately, further bleeding occurred, which resulted in a dense vitreous hemorrhage.

The left eye was monitored conservatively for several months, but showed no sign of clearing. Visual acuity in the right eye improved during this time to 20/70. On Aug. 28, 1991, the patient underwent pars plana vitrectomy in the left eye. The surgical procedure proceeded favorably, but marked preretinal fibrosis, retinal pigment epithelial atrophy, and metaplastic subretinal tissue were evident in the macula. Early preoperative cataract demonstrated progression that ultimately required extracapsular cataract and anterior chamber intraocular lens implantation, which were performed on Dec. 11, 1991.

On Jan. 23, 1992, best-corrected visual acuity was R.E.: 20/40 and L.E.: 20/300. There was no clinical sign of hemorrhage in the left macula, but there was distortion caused by preretinal fibrosis and metaplastic subsensory retinal tissue.

Focal arterial wall damage is the likely precursor of retinal artery macroaneurysms. The rarity of emboli as the cause of this damage is evident from previous reports of macroaneurysms. Some additional cases in which an embolus is noted near a macroaneurysm could have a similar origin. Palestine, Robertson, and Goldstein[3] noted that only one of ten cases had an embolus nearby. Thus, it is likely that most are not caused by embolic disease. Of course, most macroaneurysms are detected because of symptoms of loss in visual acuity. The appearance of the retinal artery before the onset of the symptoms is not known in most cases, and the potential for an undetected embolus to have preceded the macroaneurysm cannot be excluded. Emboli have been demonstrated to be the definite cause of a retinal artery macroaneurysm in three cases, including the present one.[1,5] The lack of macroaneurysms as a subsequent development in the large series of retinal artery emboli described by Arruga and Sanders[4] implies that most macroaneurysms are attributable to other causes.

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Nonbacterial Thrombotic Endocarditis and Cortical Blindness

James A. Rush, M.D.

Department of Ophthalmology, University of South Florida College of Medicine. Presented at the IX International Neuro-Ophthalmological Symposium, Williamsburg, Virginia, June 30, 1992.

Inquiries to James A. Rush, M.D., 508S Habana Ave., Suite 100, Tampa, FL 33609.

A 73-year-old man had a two-week history of stepwise painless progressive visual loss in both eyes. No focal nonvisual neurologic symptoms occurred; however, he experienced four weeks of headaches and two weeks of mild confusion. His medical history was unremarkable.

Visual acuity was R.E.: 20/200 and L.E.: counting fingers at 2 feet. He identified none of the ten City University color plates with either eye. Pupillomotor responses were brisk without afferent defect in both eyes. Results of the examination of the ocular fundi were normal bilaterally. Computed perimetry showed absolute superior altitudinal field loss with involvement of fixation, along with moderate generalized depression inferiorly in both eyes. Results of a left superficial temporal artery biopsy and bilateral carotid ultrasonograms were normal. Cranial magnetic resonance images showed a lesion in the left occipital lobe of mixed signal, suggesting hemorrhage, and mild gyral enhancement of the right occipital cortex (Fig. 1). Progressive confusion and weight and appetite loss resulted in hospitalization and death 11 days later. A chest x-ray film disclosed a left upper lobe infiltrate found on autopsy study to be a mucin-secreting pulmonary adenocarcinoma. Nonbacterial thrombotic endocarditis was present on the aortic and mitral valves, as well

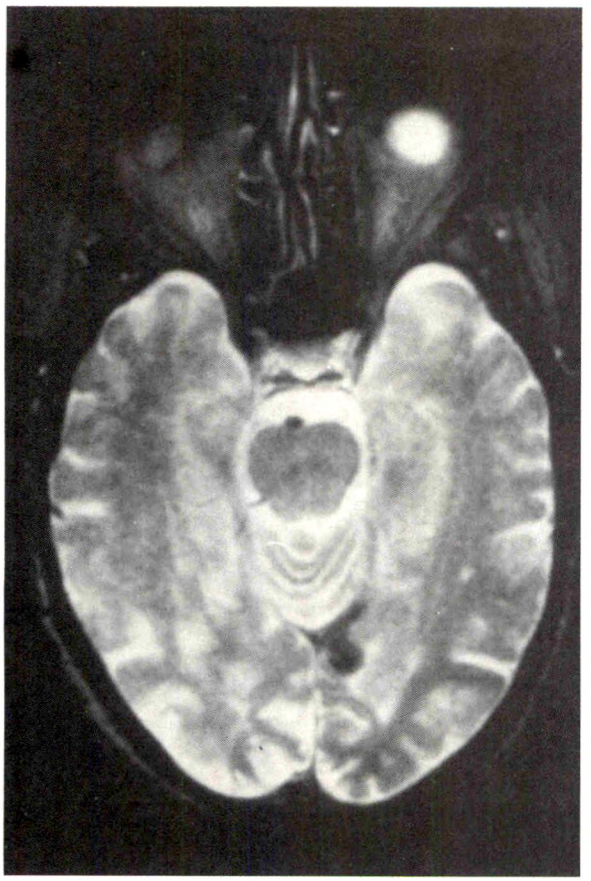


Fig. 1 (Rush). T_2-weighted image shows the round hypointense lesion in the left occipital lobe and mild gyral enhancement of the right occipital cortex.



Fig. 2 (Rush). Axial autopsy section through occipital cortex shows round area of hemorrhage in the left occipital lobe and bilateral calcarine cortical infarctions.

as in both posterior cerebral arteries, and caused multiple systemic infarctions, including those imaged on magnetic resonance scans (Fig. 2).

Occipital stroke is insufficiently recognized as a cause of visual loss in patients with cancer in whom nonbacterial thrombotic endocarditis develops. As many as 85% of patients with nonbacterial thrombotic endocarditis have underlying tumors, especially mucin-secreting adenocarcinomas of the lung and pancreas.[1] Undetectable by cardiac auscultation and conventional echocardiography because of their smaller size, the friable fibrin-platelet excrescences frequently embolize to the middle cerebral arteries and cause nonvisual stroke, which might be the initial clinical symptom of cancer.[2] Homonymous hemianopsia with ipsilateral sensory[3] or motor[4] deficits has been reported, but occipital visual loss without focal nonvisual neurologic symptoms, as in this case, might be the earliest symptom.

Nonbacterial thrombotic endocarditis should be considered in any stroke patient in whom a source of emboli cannot be found. As a remote effect of cancer on the visual system, its early detection might lead to life-prolonging anticoagulation.[5]

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Visual Recovery After Radiation Therapy of Orbital Lymphoma

Darius M. Moshfeghi, B.S.E., Paul T. Finger, M.D., Ronald B. Cohen, M.D., Woomyung Choe, M.D., and Thom Smilari, M.D.

Department of Ophthalmology, Division of Ocular Tumor and Orbital Disease, North Shore University Hospital-Cornell Medical College (D.M.M., P.T.F., R.B.C.); Department of Radiotherapy, South Nassau Community Hospital (W.C.); and Department of Pathology, North Shore University Hospital-Cornell Medical College (T.S.).

Inquiries to Paul T. Finger, M.D., Division of Ocular Tumor and Orbital Disease, North Shore University Hospital-Cornell University Medical College, 300 Community Dr., Manhasset, NY 11030.

An 84-year-old white man with glaucoma had a history of transitional cell carcinoma of the urinary bladder, disseminated well-differentiated lymphocytic follicular lymphoma, and squamous metaplasia of the prostate.

On Dec. 5, 1991, the patient had visual acuity of R.E.: 20/25 and L.E.: 20/30 (ascribed to nuclear sclerotic cataracts). On Jan. 6, 1992, he returned because of decreased vision in his left eye. Ophthalmic examination then disclosed visual acuity of R.E.: 20/30 and L.E.: no light perception. Applanation tensions were 16 mm Hg in both eyes. His pupils were miotic and nonreactive as the result of pilocarpine therapy. Both exotropia and exophthalmos were noted in his left eye. Hertel exophthalmometry showed 5 mm of proptosis at 16 mm in the right eye and 21 mm in the left eye, with a base diameter of 95 mm. Slit-lamp biomicroscopy disclosed edema of the left upper eyelid.

Computed axial tomography of the left orbit showed an ovoid area of soft tissue 3.0 cm long and 18 mm wide surrounding the left optic nerve and extending to the orbital apex (Fig. 1). Intratumoral microcalcifications were noted.

Because of the patient's desire to have prostate surgery, he was first examined in consultation on Jan. 30, 1992. Visual acuity was R.E.: 20/40 and L.E.: no light perception. Results from an ultrasonically guided fine-needle aspiration biopsy of the left orbital tumor were consistent with small cell malignant orbital lymphoma (Fig. 2).

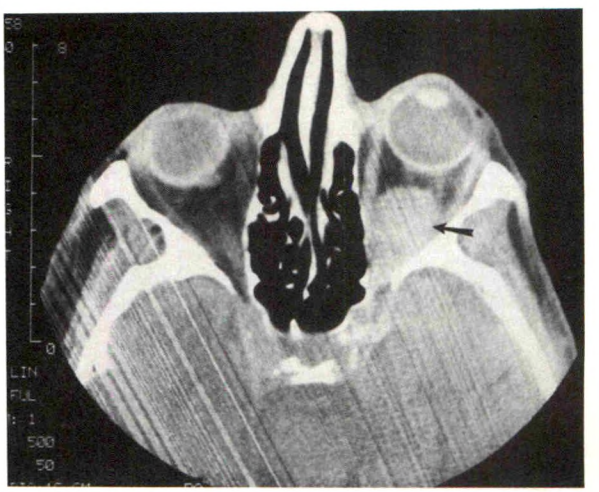


Fig. 1 (Moshfeghi and associates). Computed axial tomography shows a 3.0 × 1.8-cm tumor surrounding the optic nerve in the left eye (arrow).

Fifty-one days after documentation of the patient's loss of light perception in his left eye, external beam radiotherapy was initiated. Through a paired wedge technique, a 4 × 5-cm field, and 6-MEV photons, our patient received a total dose of 36 Gy (18 fractions of 200 cGy over a period of 24 days).

Two weeks later, visual acuity was L.E.: 20/40. The patient had normal ocular motility and decreased eyelid edema. Indirect ophthalmoscopy showed no evidence of maculopathy, vasculopathy, or optic neuropathy. Three months after treatment Hertel exophthalmometry showed symmetry at 16 mm in both eyes with a base diameter of 95 mm. Though the patient's visual acuity had stabilized at 20/40 in both eyes, relative optic nerve pallor was noted in the left eye.

Orbital lymphomas are the most common malignant orbital tumors and account for 10% of tumors of the orbit and adnexa.[1,2] Though these tumors are relatively radiosensitive (as was illustrated by our case),[3,4] it was remarkable that our patient started treatment 51 days after the first documentation of no light perception in the involved eye, and recovered to 20/40.

This case suggests that when orbital lympho-

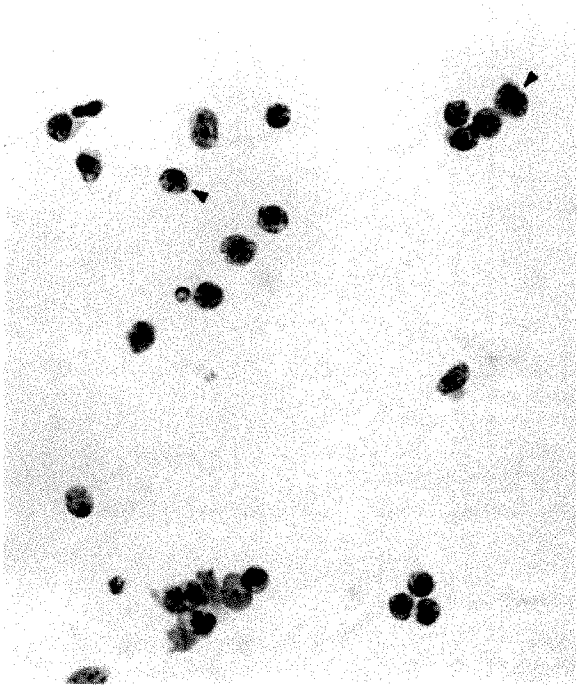


Fig. 2 (Moshfeghi and associates). Aspirate smear shows a monotonous population of small lymphocytes, some of which have cleaved nuclei (arrowheads). The tumor cells are somewhat larger than small lymphocytes with a coarsely granular chromatin pattern (×400).

ma causes optic nerve dysfunction, treatment should be initiated even after six weeks of profound visual loss.

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Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Successful Therapy for Trilateral Retinoblastoma

EDITOR:

In the article, "Successful therapy for trilateral retinoblastoma" by S. C. Nelson, H. S. Friedman, W. J. Oakes, E. C. Halperin, R. Tien, G. N. Fuller, B. Hockenberger, M. W. Scroggs, M. Moncino, J. Kurtzberg, and E. G. Buckley (Am. J. Ophthalmol. 114:23, July 1992), the report of three long-term survivors of a previously uniformly fatal disease was encouraging.

An important point regarding these patients deserves further comment. In our recent review of this disorder,[1] we noted that all previously studied patients had initial neurologic symptoms related to increased intracranial pressure and their radiographs demonstrated obstructive hydrocephalus. We speculated that these pinealomas may have been uniformly lethal because of their advanced stage at the time of diagnosis; we suggested that earlier diagnosis might improve the prognosis.

The study by Nelson and associates supports this hypothesis. The computed tomographic scans and magnetic resonance images of the patients showed no hydrocephalus. Two of the three patients had pinealomas at their initial examination. The pinealoma in the third patient was not diagnosed until approximately seven months after her initial examination. Did these patients have any neurologic abnormalities? What led to the decision to repeat computed tomography in the third patient? Have any similar patients been treated unsuccessfully, other than those from the same institution who were previously described?[2]

If none of the patients in the current article had neurologic abnormalities and no undescribed asymptomatic patients have died despite chemotherapy, then it would appear that a critical factor in successful treatment of these patients is identification of the pinealomas be-

fore they become symptomatic. This would require periodic imaging of the central nervous system of patients with heritable retinoblastoma. If such an approach were used, the imaging could be coordinated with ocular examinations, with the patient under anesthesia. If, as the authors suggest, academic centers institute a standard protocol for the treatment of these patients, then such periodic imaging would appear warranted.

GREGG T. LUEDER, M.D.
Toronto, Ontario, Canada

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Reply

EDITOR:

Dr. Lueder raises an interesting question in reference to our successful treatment of trilateral retinoblastoma. We certainly agree with the hypothesis that the earlier the diagnosis, the better the prognosis. However, we have treated several patients who were asymptomatic at the time of diagnosis in whom therapeutic interventions failed. Certainly, this is not the only factor in our successful outcomes. We do not know whether any similar patients have been treated unsuccessfully at other institutions, as these results are usually not published.

We have had a patient with bilateral retinoblastoma treated successfully with radiation at 1 year of age, who at 3 years of age was noted to have no reoccurrence intraocularly and a normal computed tomographic scan of the pineal area. Eight months later, she developed a large pineal tumor with obstructive hydrocephalus with a fatal outcome. Before this experience, we had been screening patients extensively during the first two or three years of life with neuroimaging and then semiannually thereafter. Our present protocol is to perform neuroimaging at the time of diagnosis and then every three months for the first two years, every four months for the next two years, and then every six months until the age of 5 years. This coincides with our ocular examinations and is coordinated effectively on the same day.

We hope that efforts can be made to standardize the treatment of these patients, as it is only through such efforts that we be able to advance our knowledge and provide the best possible care.

STEVEN C. NELSON, M.D.
HENRY S. FRIEDMAN, M.D.
W. JERRY OAKES, M.D.
EDWARD C. HALPERIN, M.D.
ROBERT TIEN, M.D.
GREGORY N. FULLER, M.D.
BEVERLY HOCKENBERGER
MARK W. SCROGGS, M.D.
Durham, North Carolina
MARK MONCINO, M.D.
Louisville, Kentucky
JOANNE KURTZBERG, M.D.
EDWARD G. BUCKLEY, M.D.
Durham, North Carolina

Successful Therapy for Trilateral Retinoblastoma

EDITOR:

In the article, "Successful therapy for trilateral retinoblastoma," by S. C. Nelson, H. S. Friedman, W. J. Oakes, E. C. Halperin, R. Tien, G. N. Fuller, B. Hockenberger, M. W. Scroggs, M. Moncino, J. Kurtzberg, and E. G. Buckley (Am. J. Ophthalmol. 114:23, July 1992), two points deserve additional comment. Patients with pinealoblastoma (with or without retinoblastoma) die because of neuroaxis spread of tumor.[1] If the tumor is diagnosed and treated before dissemination of cerebrospinal fluid, cures are more likely. The good results in these three patients may represent the fortunate opportunity of these physicians to diagnose a pineal tumor that had not yet metastasized. Therefore, it was the stage of disease and not the specific therapy that allowed successful treatment.

The authors' case with the longest follow-up never had histologic documentation. Although it may have been a pinealoblastoma, patients with retinoblastoma do develop other curious central nervous system lesions that may respond to chemotherapy.

If any of the three patients has recurrence of

tumor or dies, I hope the authors will write a note to THE JOURNAL to keep us up to date.

DAVID H. ABRAMSON, M.D.
New York, New York

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Reply

EDITOR:

Dr. Abramson raises several points with regard to our successful treatment of trilateral retinoblastoma. He concludes that it was the stage of the disease rather than the therapy that allowed successful treatment. We have no way of knowing whether this is true. Previous investigators have not been able to prevent a fatal outcome in patients with trilateral retinoblastoma regardless of the stage of the tumor when first symptomatic. Although treatment before cerebral spinal fluid dissemination may make a cure more likely, there is currently no evidence that diagnosing trilateral retinoblastoma before neuroaxis spread will result in a cure. We hope that further investigation will allow us to answer this question.

Although our patient with the longest follow-up never had histologic documentation, it is difficult to fathom that a patient with bilateral retinoblastoma and a tumor in the pineal region does not have trilateral retinoblastoma. We have not encountered any report of another type of tumor in the pineal region in a patient with retinoblastoma.

We will certainly continue to follow up these patients, because we believe they represent a unique group that will advance our understanding of trilateral retinoblastoma.

STEPHEN C. NELSON, M.D.
HENRY S. FRIEDMAN, M.D.
W. JERRY OAKES, M.D.
EDWARD C. HALPERIN, M.D.
ROBERT TIEN, M.D.
GREGORY N. FULLER, M.D.
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Durham, North Carolina
MARK MONCINO, M.D.
Louisville, Kentucky
JOANNE KURTZBERG, M.D.
EDWARD G. BUCKLEY, M.D.
Durham, North Carolina

Multifunction Endolaser Probe

EDITOR:

In the article, "Multifunction endolaser probe," by G. A. Peyman and K. J. Lee (Am. J. Ophthalmol. 114:103, July 1992), the authors describe this laser probe as their design without acknowledging that it is a modification of an endolaser probe developed and already marketed by Infinitech, Inc. (St. Louis, Missouri).

In the spring of 1991, I initiated collaboration with the engineering staff at Infinitech, Inc., to develop an aspirating laser probe. The probe was subsequently marketed by Infinitech, Inc., beginning in January 1992, under the name "Chang aspirating laser probe." This probe has all of the backflush, aspiration, and infusion capabilities described by Peyman and Lee, neither of whom was involved in the design of the instrument. The probe design was modified later to incorporate a light fiber when Dr. Peyman requested the addition of fiberoptic light as an added function.

While the instrument described by Peyman and Lee is a modification of the probe that carries my name, the appearance and laser, aspiration/infusion capabilities are identical to the Chang aspirating laser probe. The casual reader might even be led to believe that I have plagiarized the ideas of Drs. Peyman and Lee, because the probe sold under my name has the same appearance. I simply would like to set the record straight by clarifying the history behind the development of this instrument.

STANLEY CHANG, M.D.
New York, New York

Reply

EDITOR:

In April 1988, Dr. Raichand, and one of us (G.A.P.) visited Advanced Surgical Products, Inc. (St. Louis, Missouri), to discuss development of various surgical instruments with this company. Among the items discussed with Mr. Gregg Scheller, Vice President-Marketing, Mr. James Easley, and Mr. Todd Hessel was the development of an endolaser system with multifunction capabilities. On April 29, 1988, Mr. Gregg Scheller (written communication) confirmed their commitment to the development of various products and went on to specify the concept of "combined laser, illumination, and suction in the same instrument." He wrote: "This correspondence will serve as legal evidence that the innovative ideas above, with the exception of the scissors handpiece, were supplied by you."

By the end of 1989, Infinitech, Inc., (St. Louis, Missouri), acquired Advanced Surgical Products, Inc., and all its employees, including Messrs. Scheller, Easley, and Hessel, who became a part of Infinitech, Inc., until the present. Because of this transition, a number of projects that I had proposed to Advanced Surgical Products, Inc., were put on hold. Subsequently, in 1990, in collaboration with Donald D'Amico, M.D., and Iris Medical Instruments (Mountain View, California), we developed an endolaser probe with aspiration capability.[1]

Knowing that there was still merit to the original concept of multifunction endolaser probe, I contacted Mr. Gregg Scheller from Infinitech, Inc., in 1991, and asked if the company could produce this probe for me, which they agreed to do.

Dr. Chang may have had the idea of an aspirating laser probe in the spring of 1991, but certainly it did not predate the probe designed by Dr. D'Amico and me, or my original concept of a combined laser, illumination, and suction instrument, as described in the Letter to The Journal.

GHOLAM A. PEYMAN, M.D
KWANG J. LEE, M.D.
New Orleans, Louisiana

Reference

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The Obligation of Ophthalmic Organizations to Report Their Actions

EDITOR:

Congratulations for publishing the editorial, "The obligation of ophthalmic organizations to report their actions," by F. W. Newell (Am. J. Ophthalmol. 114:220, August 1992). The issue Dr. Newell addresses is an important one. Ophthalmology is not just fragmented by subspecialty. but by other categories as well: academicians. basic researchers, HMO physicians, ambulatory surgeons, general office practitioners, and the like. The more the organizations representing these somewhat different interests talk to themselves alone, and the less they talk to others, the more serious their fragmentation becomes, with the development of unnecessary jealousies, resentments, and rivalries.

Being open and honest is neither always easy nor without risk. But not to be open and honest guarantees a disconnectedness from each other that results in our losing the collegiality essential for the well-being of ophthalmology as an integral part of the medical profession as a whole.

GEORGE L. SPAETH, M.D.
Philadelphia, Pennsylvania

BOOK REVIEWS

Edited by Mark J. Mannis, M.D.

Ocular Emergencies. By Robert A. Catalano. Philadelphia, W. B. Saunders, 1992. 550 pages, Index, illustrated. $45

Reviewed by DAVID CHAFFIN
Sacramento, California

The beginning of any residency program is a challenging time. Often, novice ophthalmology and emergency room residents are responsible for treating patients with ocular and orbital emergencies. Unfamiliarity with this aspect of one's newly chosen field can provoke great anxiety. Dr. Catalano's well-written book helps to ease some of the anxiety and uncertainty associated with the residency training. It provides a wonderful reference for physicians interested in the examination and treatment of patients with ocular and orbital emergencies.

The text is divided into four sections. It begins with a review of examination techniques and diagnostic modalities that are useful in the emergency room. Special attention is directed to the use of diagnostic tests and findings that might be expected in common disorders. The author devotes a separate section to examination techniques in the pediatric patient. This section is clearly written, well organized, and of great practical value not only in the emergency room but in the clinic as well.

The remainder of the book is concerned with the examination and treatment of a variety of ocular emergencies. These are divided into the following three categories: traumatic, nontraumatic, and infectious and inflammatory. Traumatic disorders are classified according to the structures involved. Nontraumatic disorders are classified into disorders whose cause is readily apparent and those with nonspecific and nonlocalizing symptoms. Separate chapters describe neuro-ophthalmologic and retinal disorders in detail. Individual chapters are devoted to the patient with sudden loss of vision and to the patient with functional visual loss. Cross-reference is abundant, and there are numerous tables with practical, quick-reference information. The frequent step-by-step flow charts are particularly useful in establishing a diagnosis and formulating appropriate treatment plans.

The text is accompanied by 281 black-and-white illustrations, an appendix that outlines common abbreviations in ophthalmology, and a well-organized, easily accessible index. If there is one negative aspect of this book, it might be the poor quality of some of the black-and-white photographs.

Dr. Catalano successfully meets his goals of providing the beginning resident with the informational tools necessary for evaluating and treating ocular and orbital emergencies. This text is important reading for beginning ophthalmology and emergency residents and it is a useful reference for any physician interested in evaluating and treating ocular and orbital emergencies.

Optics and Refraction. A User-Friendly Guide. By David Miller. Textbook of Ophthalmology, vol. 1. Edited by Steven M. Podos and Myron Yanoff. New York, New York, Raven Press, 1991. 268 pages, Index, Illustrated. $85

Reviewed by DAVID L. GUYTON
Baltimore, Maryland

For this first volume of an ambitious, new, ten-volume textbook of ophthalmology, Dr. Miller presents ophthalmic optics in an entertaining and effective manner, using intuitive rather than mathematical arguments. He uses familiar clinical examples to illustrate optical principles and gives historical vignettes that rekindle the excitement of invention to maintain the interest of the reader.

The book is not comprehensive, for only smatterings of basic geometric optics are included. Such information is easily available elsewhere, however, and Dr. Miller has used this opportunity to illuminate many of the more difficult areas of clinical optics such as physical optics, lasers, light units, and contrast sensitivity testing. He strikes a balance between exact exposition and entertaining prose, appropriately referencing specific points. He includes an excellent chapter on ophthalmic instruments and up-to-date discussions on ocular light damage, laser-tissue interactions, and the basics of corneal refractive surgery. Three superb chapters have been contributed by others: "Subjective Testing of Refraction," by Borish; "Spectacle Lenses," by Milder; and "Contact Lenses," by Keating.

The volume contains almost 250 illustrations, mostly in color and handsomely done. In an effort to simplify the illustrations, however, there has been mislabeling or inaccurate optical diagrams in several figures. In several instances the text does not correlate with the illustrations.

There are a few errors. For example, retinoscopic findings are compensated in the wrong direction for the working distance. The statement is made that high-power, hand-held lenses amplify small changes in retinal topography in indirect ophthalmoscopy, whereas the opposite is true. One could also take issue with the statement that high-power correcting cylinders call for high-power cross cylinders during subjective refraction (rather than basing the cross-cylinder power on the visual acuity level at the time of application).

These occasional errors do not, however, detract significantly from the overall value of the book. It is a remarkably readable and informative text, unique in the field. It cannot serve as a primary text on ophthalmic optics because of the lack of basic geometric optics, but it does serve as an excellent supplement to other sources, a supplement which is well worth reading by residents and practitioners alike. I thoroughly enjoyed it.

Atlas of Ophthalmic Surgery, volume II. Oculoplastic, Lacrimal, and Orbital Surgery. By Jonathan J. Dutton. St. Louis, Mosby Year Book, Inc., 1992. 342 pages, index, illustrated. $125

Reviewed by RICHARD BENSINGER
Seattle, Washington

This atlas, the second volume of a series on ophthalmic surgery, is devoted to the standard techniques of oculoplastic surgery. This text is not a comprehensive review in the rapidly evolving field of ophthalmic plastic surgery. Instead, the author has carefully chosen standard surgical techniques, which have stood the test of time and usefulness. In the preface, he states that his audience is not the oculoplastic sophisticate, but rather the less specialized ophthalmic surgeon who might be expected to perform the illustrated procedures infrequently.

The book is organized into the following three major divisions: eyelid surgery, lacrimal surgery, and orbital surgery. Each is then subdivided into sections on specific surgical procedures prefaced by a concise summary of the anatomy and pathologic characteristics of the relevant region. These discussions are logical and orderly, and they provide an effective surgical anatomic orientation.

The most valuable feature is the carefully illustrated section outlining each surgical technique. The color illustrations, displayed from the point of view of the surgeon, are carefully researched and clearly presented. I predict that these illustrations will become standard for teachers of ophthalmic surgical techniques.

This book is not the place to search for the most appropriate among alternative techniques. If, however, the procedure you have chosen is depicted here, there is hardly a better place to find the required details. Especially helpful are numerous cross-sectional views showing depth of suture placement and the layers in the plane of surgical exposure. This feature clarifies points so often confusing in other atlases of ophthalmic surgery.

This book should find a place in all teaching and instructional collections. It accomplishes the stated aims of the author well. The medical illustrator, Thomas Waldrop, is to be especially congratulated.

The Lazy Eye. A Simulation Environment for Neuro-Ophthalmology. Computer software. By Howard S. Bregman, Phong T. Ly, and Steven Galetta. Bluebell, Pennsylvania, Keyboard Publishing, 1992. (No price given)

Reviewed by R. D. CUNNINGHAM
Temple, Texas

Except for its somewhat misleading title (this program is not about amblyopia), this is an excellent interactive teaching program for the beginning student in neuro-ophthalmology, medical student, resident, or anyone interested in pupillary and neuromotility disorders.

The program, which requires a Macintosh computer (preferably a Mac II, SE30, or higher system) with 2 megabytes of RAM and HyperCard Version 1.0 or higher, allows the student to perform a simulated ocular examination on a normal person as well as on patients with a variety of disorders of ocular motility and pupillary function. Many significant motility disorders are included, including oculomotor, trochlear, and trigeminal nerve palsies; gaze palsies; and nystagmus syndromes. The user-controlled graphics are astonishingly realistic.

Each disorder is supplied with a display of the underlying anatomy and pertinent clinical information. For many of the conditions described, a literature citation is also provided to allow the student to pursue the subject further. Normal pupillary reactions are graphically displayed, and most of the common abnormal pupillary conditions are included. The program allows the pupils to be viewed in dim or bright light, and the action of various pharmacologic agents is demonstrated. The pertinent anatomic substrate of the pupillary reactions is included.

The history and physical findings are described for six patients with specific neurologic conditions. Questions follow a brief clinical discussion. The questions concerning patient examination and treatment are such that the student should be able to answer. This clinical simulation format is logical and appropriate, and students would be wise to emulate this method in their approach to clinical problems.

The program requires only a minimum knowledge of computer use to navigate the material successfully. One minor complaint I have is that the graphics do not display the eyelid position, which is important in some of the disorders (for example, Duane's retraction syndrome and Horner's syndrome). The Lazy Eye is intended to be a growing program with an expanding library of features and conditions. This will allow the addition of conditions such as myasthenia gravis, Graves' ophthalmoplegia, progressive supranuclear palsy, and others, which are not in the present program.

This is by no means an exhaustive compilation of pupil and neuromotility disorders, but it is an excellent introduction for the student. It contains accurate and well-presented information. It should be valuable for the teacher who frequently does not have clinical material available to show students. My guess is that students will find this program not only informative, but fun.

The Fragile Species. By Lewis Thomas. New York, New York, Macmillan Publishing Company, Inc., 1992. 193 pages. $20

Reviewed by H. STANLEY THOMPSON
Iowa City, Iowa

This is a book of short essays by a thoughtful, articulate physician-scientist who writes beautifully and can make ideas sparkle. The essays are about some of the major medical issues of our time: AIDS, drug abuse, and aging. They are also about the author's concern for the fragile biosphere that surrounds our home planet—that living, breathing organism of which we are a part. He is captivated by recent work suggesting that the earliest forms of life on our planet were bacteria and finds it fascinating that three or four billion years ago these archaebacteria learned how to use DNA to encode instructions for growth and development, the very same skills used today by grasses, grasshoppers, grass-eaters, and grass-smokers. He is completely enchanted by the thought that we are descended from bacteria and that mitochondria are almost-but-not-quite free-living microbes within our every cell. "Is the human body," he asks, "just a sort of ornamented carapace for colonies of bacteria?"

In another essay, Dr. Thomas examines the work in psychology on intracranial self-stimulation: an area of study that began with James Olds's identification of a "pleasure center" in the brains of rats which, when stimulated, kept the animals fully occupied. Thomas allows himself to speculate that a pleasure center may be present in all forms of life and that its stimulation may represent, quite simply, the pleasure of being alive. His own pleasure center seems to be tweaked when "that word (appears) in that line of that poem," and " . . . in the fourth movement of the Missa Solemnis, where the violin and the human voice suddenly turn into a single voice. . . ."

Elsewhere he talks about how the word "holistic" has lost its respectability. He skewers "holistic medicine" by saying that it seems to him to be "an effort to give science the heave-ho out of medicine and to forget all about the working parts of the body and get along with any old wild guess about disease." It is obvious, he believes, that any living organism is something more than the sum of its working parts. Science itself is a "holistic" enterprise. He concedes that a new word is needed for this concept.

This is the voice of one whose life has been guided by the respect for science that he learned in his youth. And what a delightful mind is behind the voice—it must be happiest when busy. Even in neutral it is fiddling with Fibonacci numbers! You will enjoy meeting Dr. Thomas's mind. It is rich with grace and warmth.

Books Received

Decision Making in Ophthalmology. Edited by W. A. J. van Heuven and Johan T. Zwaan. St. Louis, Mosby Year Book, 1992. 318 pages, index, illustrated. $65

This is one of a series of books intended to provide the clinician with practical algorithms, or decision trees, that are useful in the diagnosis and management of clinical problems. This multi-contributor text contains 130 ophthalmologic decision trees involving problems in general ophthalmology, oculoplastics, pediatric ophthalmology, corneal disease, glaucoma, lens disorders, vitreoretinal disease, uveitis, and neuro-ophthalmology. Each problem (for example, dry eye, leukocoria, poor vision after cataract surgery) is elucidated by a graphic tree as well as text that is referenced to specific items on the tree explaining or amplifying those items. Leafing through this book will convince the clinician that it may be most useful in the daily practice of ophthalmology when our own mental diagnostic trees are usually not as thorough or well thought out as those in this book. Though not a conventional text, it is sure to be frequently used by the ophthalmologist at every professional level.

Enzymology of The Tears. By Andras Berta. Ft. Lauderdale, Florida, CRC Press, Inc., 1992. 328 pages, index, illustrated. $149.95

This volume is an exhaustive monograph on the protein content of the tear film. Beginning with chapters on the anatomy and physiology of the lacrimal system and the tear film, the remainder of the book deals with the panoply of polypeptides found in human tears. Included in the discussion are lysozyme, collagenases, the plasminogen activator-plasmin system, and a variety of others. The author then relates tear enzymes to an array of clinical problems such as wound healing, viral infections, allergic disease, and contact lenses. This scholarly monograph will be of use to anyone involved in an in-depth study of the tear system.

Fundamentals of Ophthalmic Practice. Ethics and Economics. Office and Risk Management. By Stephan A. Kamenotzky. New York, New York, Raven Press, 1992. 143 pages, Index, Illustrated. $39.95

Intended primarily for residents and new practitioners, this book aims to identify common office practice problems and help the ophthalmologist avoid them. The book is divided into five sections: ethics, socioeconomic considerations, risk management and malpractice, starting and developing a practice, and practice cash-flow management. This is a helpful volume from which even the established practitioner can learn something. The unique quality of this book is that it juxtaposes, thoughtfully, ethical and socioeconomic issues and the practical problems of ophthalmology-specific office management. There is good information here for today's ophthalmic practitioner at a time when the structure of American medical practice has required us to pay close attention to more global economic issues, government intervention, the strong hand of the insurers, and contract medicine.

Management and Treatment of Benign Cutaneous Vascular Lesions. Edited by Oon Tian Tan. York, Pennsylvania, Williams & Wilkins, 1992. 192 pages, index, illustrated. (No price given)

Seventeen contributors including otolaryngologists, ophthalmologists, dermatologists, surgeons, pathologists, anesthesiologists, an occupational therapist, and basic scientists have collaborated under the editorship of Oon Tian Tan to produce a handsomely crafted treatise on the management of benign cutaneous vascular lesions. The book contains chapters on virtually every aspect of these lesions ranging from their classification to modes of treatment, with special emphasis on laser treatment. This volume will be of primary interest to the dermatologist. However, the oculoplastic surgeon or pediatric ophthalmologist will find the information in this book worthwhile.

ABSTRACT DEPARTMENT

Edited by George B. Bartley, M.D.

Alternative solution for Opticrom. Fiscella, R. G.*, Siegel, F. P., and Welsbecker, C.: Am. J. Hosp. Pharm. 49:70, 1992.

The authors described the use of a nasal solution of 4% cromolyn sodium (Nasalcrom, Fisons Corporation, Rochester, New York) as a substitute for the ophthalmic solution, Opticrom (Fisons Corporation), which has been commercially unavailable in the United States for several months. The sole difference between the two products is the concentration of the preservative, ethylenediaminetetra-acetate: 0.1% in the ophthalmic solution and 0.01% in the nasal solution. The concentration of benzalkonium chloride is identical for each solution (0.01%). To ensure sterility of the product for ophthalmic use, the nasal solution is aseptically filtered through a 0.22-μm filter into a sterile dropper bottle within a laminar airflow hood. Additionally, the authors recommended that the solution be refrigerated and discarded after one month. No adverse effects from the use of the alternative product have been reported.—George B. Bartley

*University of Illinois at Chicago Eye Center, 1855 W. Taylor, Chicago, IL 60612.

Conjunctival impression cytology with transfer as a field-applicable indicator of vitamin A status for mass screening. Carlier, C.*, Coste, J., Etchepare, M., and Amédée-Manesme, O.: Int. J. Epidemiol. 21:373, 1992.

Vitamin A deficiency affects an estimated 20 to 40 million children worldwide. The World Health Organization has defined xerophthalmia and decreased serum vitamin A concentration as prevalence criteria for vitamin A deficiency of public health importance. The authors used a simplified conjunctival impression cytology technique to detect the disappearance of goblet cells or the enlargement of epithelial cells, which are indicators of early vitamin A deficiency, among 1,451 children in rural Senegal. The three following classifications of results were proposed: deficient-nondeficient, positive-negative, and abnormal-normal. Intraobserver reliability was evaluated with Cohen's unweighted kappa test and validity was assessed by sensitivity and specificity by using serum retinol concentrations. Reliability and sensitivity were highest for the abnormal-normal classification (kappa = 0.91, 95% confidence interval: 0.89 to 0.93; sensitivity = 74%, 95% confidence interval: 66% to 82%). The authors concluded that conjunctival impression cytology with transfer is an inexpensive, noninvasive, and simple screening test and proposed that vitamin A deficiency for public health purposes be defined as 50% of the abnormal cytologic test result.—George B. Bartley

*Institut National de la Santé et de la Recherche Médicale, Unité 56, Hôpital de Bicêtre, 78 av du Gal Leclerc, 94275 Le Kremlin-Bicêtre, France.

Prevalence of mitral valve prolapse in keratoconus patients. Sharif, K. W.*, Casey, T. A., and Coltart, J.: J. R. Soc. Med. 85:446, 1992.

Fifty patients with keratoconus that required penetrating keratoplasty were screened for mitral valve prolapse by two-dimensional echocardiography with color flow Doppler studies. Thirty-two males and 18 females were studied; the patients ranged in age from 17 to 64 years (mean, 32 years) and had no ocular disorders other than keratoconus, no systemic collagen diseases, and no history of cardiac dysfunction. Mitral valve prolapse was found in 29 of the 50 patients with keratoconus, compared to three of 50 age- and gender-matched control subjects. The authors believed that the clinical, histopathologic, and biochemical similarities between keratoconus and mitral valve prolapse suggest that the two disorders may be different manifestations of similar defects in collagen metabolism. Conceivably, a single event during embryogenesis may affect both the corneal stroma and the atrioventricular valves because both structures form during the sixth to seventh week of fetal life.—George B. Bartley

*Ophthalmology Department, Jordan University Hospital, P.O. Box 13046, Amman, Jordan.

Corneal arcus and cardiovascular risk factors in Asians in Singapore. Hughes, K.*, Lun, K. C., Sothy, S. P., Thai, A. C., Leong, W. P., and Yeo, P. B.: Int. J. Epidemiol. 21:473, 1992.

The presence of grossly detectable corneal arcus was determined in a cross-sectional, random survey of Chinese, Malay, and Indian subjects aged 18 to 69 years. The prevalence rates increased with age, ranging from 0.5% (two of 403) and 0.3% (one of 379) for men and women, respectively, in the 18- to 29-year age group, to 70.7% (152 of 215) and 55.3% (94 of 170) for men and women, respectively, aged 50 to 69 years. In the 30- to 49-year age group, persons with arcus had significantly higher serum low-density lipoprotein-cholesterol concentrations than individuals without arcus ($P < .05$ for men and $< .001$ for women). Corneal arcus in persons younger than 50 years increased the likelihood of having serum low-density lipoprotein-cholesterol values above normal to 1.8 for men and 2.6 for women. No association was found between corneal arcus and serum high-density lipoprotein-cholesterol, serum fasting triglyceride, blood pressure, or cigarette smoking. The authors concluded that although the development of corneal arcus is primarily age-related, increased serum low-density lipoprotein-cholesterol accelerates the process and is partially responsible for the association of arcus with coronary heart disease.—George B. Bartley

*Department of Community, Occupational and Family Medicine, National University of Singapore, National University Hospital, Lower Kent Ridge Rd., Singapore 0511.

A prospective study of cigarette smoking and risk of cataract in men. Christen, W. G., Manson, J. E., Seddon, J. M., Glynn, R. J., Buring, J. E., Rosner, B., and Hennekens, C. H.*: JAMA 268:989, 1992.

Of 22,071 male physicians aged 40 to 84 years in the Physicians' Health Study, risk factor information was available for 17,824 subjects who did not report cataract at baseline. During a follow-up interval of 60 months, 557 incident cataracts among 371 physicians were confirmed. Cataract was defined as an age-related lens opacity that was responsible for a decrease in best-corrected visual acuity to 20/30 or worse. A nuclear sclerotic cataract was present in 442 eyes, whereas a posterior subcapsular cataract developed in 204 eyes. Compared with subjects who had never smoked, current smokers of 20 or more cigarettes per day had a significant increase in the risk of cataract [relative risk [RR], 2.16; 95% confidence interval, 1.46 to 3.20; $P < .001$). Similar results were found after other potential cataract risk factors were controlled in a logistic regression model. Current smokers of 20 or more cigarettes daily had significant increases in nuclear sclerosis (RR, 2.24; 95% confidence interval, 1.47 to 3.41; $P < .001$) and posterior subcapsular cataract (RR, 3.17; 95% confidence interval, 1.81 to 5.53; $P < .001$). Past smokers had an increased but not statistically significant risk of posterior subcapsular cataracts but not of nuclear sclerosis. No increased risk of cataract was found for current smokers of less than 20 cigarettes daily. The data support the hypothesis that cigarette smoking increases the risk of developing both nuclear sclerotic and posterior subcapsular cataract.—George B. Bartley

*Channing Laboratory, 900 Commonwealth Ave. E., Boston, MA 02215.

A prospective study of cigarette smoking and risk of cataract surgery in women. Hankinson, S. E.*, Willett, W. C., Colditz, G. A., Seddon, J. M., Rosner, B., Speizer, F. E., and Stampfer, M. J.: JAMA 268:994, 1992.

The incidence of cataract extraction for age-related lens opacities was determined from data in the Nurses' Health Study. By 1980, 50,828 women had been enrolled in the study and additional subjects were added as they became 45 years of age. Four hundred ninety-three cataracts were extracted during 470,302 person-years of follow-up. Among women with at least a 65 pack-year smoking history, the age-adjusted relative risk (RR) was 1.63 (95% confidence interval, 1.18 to 2.26; P for trend = .02). The relative risk of cataract extraction was similarly increased in relation to the number of cigarettes smoked currently or in the past. Smoking was associated in particular with posterior subcapsular cataracts among subjects with a smoking history of $\geq$65 pack-years (RR, 2.59; 95% confidence interval, 1.49 to 4.50).

The authors concluded that cigarette smoking increases the risk of cataract extraction.—George B. Bartley

*Channing Laboratory, 180 Longwood Ave., Boston, MA 02115.

Scotopic spectral sensitivity of phakic and aphakic observers extending into the near ultraviolet. Griswold, M. S., and Stark, W. S.*: Vision Res. 32:1739, 1992.

Despite interest in ultraviolet (UV) damage and UV vision in lower vertebrates, there are few recent publications on human UV sensitivity. We obtained dark-adapted spectra from 4 aphakic and 5 normal eyes at 8.8° off-fovea using the staircase method. Our measurements extended from 314.5 nm, near the limit imposed by corneal UV absorbance, to 650 nm. Phakic and aphakic sensitivities resembled the traditional rod spectrum at long wavelengths with a peak around 500 nm. However, aphakic subjects were much more sensitive than phakic observers below 420 nm. From phakic volunteers ranging in age from 22 to 43 we deduced lens absorbance which depressed sensitivity at 350 nm by approx. 4 log units (N = 7 phakic runs on 5 eyes, average age = 30) as expected. We show a maximum lens absorbance at 355–360 nm and a UV window in the lens absorbance at 315 nm consistent with data on optical density of human lenses.—Authors' abstract

*Department of Biology, 3507 Laclede Ave., St. Louis, MO 63103.

Factors related to the final visual outcome of 425 patients with traumatic hyphaema. Ng, C. S.*, Sparrow, J. M., Strong, N. P., and Rosenthal, A. R.: Eye 6:305, 1992.

Factors related to the incidence of secondary haemorrhage in 462 patients with traumatic hyphema. Ng, C. S.*, Strong, N. P., Sparrow, J. M., and Rosenthal, A. R.: Eye 6:308, 1992.

The authors reviewed the records of patients who had been admitted for blunt ocular trauma with hyphema. In the first report, significant predictors of a worse final visual acuity were the size of the hyphema when the patient was initially examined (P = .00003) and the presence of retinal damage (P = .00001). Neither treatment with topical corticosteroids or cycloplegic agents nor the occurrence of a secondary hemorrhage influenced the final visual outcome when other variables had been considered. In the second report, a secondary hemorrhage occurred in 40 of 462 (8.7%) inpatients. The size of the initial hyphema and the presence of concomitant retinal damage did not affect the incidence of secondary hemorrhage. Although treatment with topical corticosteroids decreased the incidence of rebleeding by approximately one half (P = .005), the administration of cycloplegic eyedrops had no effect.—George B. Bartley

*Department of Ophthalmology, Leicester Royal Infirmary, Leicester LE1 5WW, England.

Oral administration of tranexamic acid in the management of traumatic hyphema in children. Deans, R., Noël, L.-P.*, and Clarke, W. N.: Can. J. Ophthalmol. 27:181, 1992.

One hundred sixty-three patients aged 17 years or less who had a hyphema from blunt trauma were treated with oral tranexamic acid, 25 mg/kg of body weight (maximum, 1,500 mg), every eight hours for five days. All patients were hospitalized and confined to bed with the head elevated, and in most patients the affected eye was patched. Topical corticosteroids or cycloplegics "were prescribed at the discretion of the attending ophthalmologist." A secondary hemorrhage occurred in five patients (3%), all of whom had an initial hyphema that filled one third or less of the anterior chamber. The rebleeding rate was significantly less than in a control population of 316 patients who had been treated similarly but without an oral antifibrinolytic agent at the same hospital during an earlier time period (secondary hemorrhage in 24 of 316 patients; P = .008). No side effects were noted in patients treated with tranexamic acid, which has been reported to be ten times more potent than aminocaproic acid. Although tranexamic acid has been used for nearly 20 years in Canada and Europe, the medication is

not approved for ophthalmic use in the United States.—George B. Bartley

*Department of Ophthalmology, Children's Hospital of Eastern Ontario, 401 Smyth Rd., Ottawa, ON K1H 8L1, Canada.

Systemic antiviral drugs used in ophthalmology. Teich, S. A., Cheung, T. W., and Friedman, A. H.*: Surv. Ophthalmol. 37:19, 1992.

Antiviral therapy is useful in the treatment of herpes simplex and herpes zoster infections, acute retinal necrosis syndrome, cytomegalovirus retinitis, and human immunodeficiency virus infections. In this comprehensive review (474 references), the authors described the mechanism of action, pharmacology, toxicity, and systemic and ocular uses of the four major antiviral drugs of ophthalmic importance: vidarabine, acyclovir, ganciclovir, and foscarnet. Additionally, zidovudine, didanosine, dideoxycytidine, interferons, immunoglobulin therapy, and newer experimental drugs were reviewed.—George B. Bartley

*Department of Ophthalmology, Mt. Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029.

Role of HIV and CMV in the pathogenesis of retinitis and retinal vasculopathy in AIDS patients. Faber, D. W., Wiley, C. A., Lynn, G. B., Gross, J. G., and Freeman, W. R.*: Invest. Ophthalmol. Vis. Sci. 33:2345, 1992.

Cotton-wool spots and cytomegalovirus (CMV) retinitis are seen frequently in AIDS patients. Human immunodeficiency virus (HIV) infection of the retina has been proposed as a mechanism for the high incidence of retinal pathology. An autopsy study of the eyes from 25 consecutive cases of AIDS was performed using gross examination, light microscopy, trypsin digestion of retinal vasculatures, and immunohistochemistry to evaluate the possible role of HIV, as well as CMV, in the pathogenesis of retinitis and retinal vasculopathy. Brain tissue was studied in the first 20 of these cases to evaluate any correlation between retinal and central nervous system pathology. CMV retinitis was observed in 15 cases (60%). Cotton-wool spots were seen in nine cases (36%). CMV encephalitis was detected in four cases, whereas HIV encephalitis was noted in five cases. We were unable to demonstrate a correlation between CMV retinitis and CMV encephalitis. However, the number of cases studied was small, and the frequency of CMV encephalitis was low. On the other hand, bilateral CMV retinitis demonstrated a correlation to HIV encephalitis ($P < 0.005$, Fisher's exact test). HIV infection of the retina was not detected by typical morphologic changes or immunohistochemistry. Immunohistochemistry localized CMV infection solely to areas of active retinitis. These findings suggest that bilateral CMV may serve as a marker of HIV encephalitis, possibly indicating a severely immunodepressed state. In addition, it appears that pathologically significant HIV infection of the retinal vascular endothelium that results in arteriolar occlusion or breakdown of the blood-retinal barrier does not occur frequently enough to account for the high incidence of cotton-wool spots and CMV retinitis seen in AIDS patients.—Authors' abstract

*Shiley Eye Center, University of California, San Diego, La Jolla, CA 92093.

Detection of colour vision abnormalities in uncomplicated type 1 diabetic patients with angiographically normal retinas. Hardy, K. J.*, Lipton, J., Scase, M. O., Foster, D. H., and Scarpello, J. H. B.: Br. J. Ophthalmol. 76:461, 1992.

Diabetic patients with retinopathy may have abnormal color discrimination. The authors studied 38 patients with type 1 diabetes in whom fluorescein angiographic and fundus photographic results were normal to determine if color vision may be defective in patients without overt vascular disease. The patients ranged in age from 16 to 40 years, were taking no medications other than insulin, and had no evidence of cataract, hypertension, or nephropathy. Although each patient scored normally on the Ishihara 38-plate test and the City University Test, 57% (22 of 38 patients) of the diabetic patients had Farnsworth-Munsell 100-hue test error scores more than two standard deviations above the mean compared with an age-matched control group ($P < .001$). There was no rela-

tionship between color vision abnormalities and diabetes duration, blood glucose at the time of color vision testing, or the most recent or average glycosylated hemoglobin results. The authors concluded that color discrimination may be abnormal from nonvascular causes in patients with uncomplicated type 1 diabetes before the onset of apparent retinopathy. Possible etiologic mechanisms include osmotic retinal distortion and disordered metabolism of neural cells.—George B. Bartley

*Department of Medicine, Division of Endocrinology and Metabolism, University of New Mexico, Albuquerque, NM 87131.

Fundus hemorrhages in infancy. Kaur, B., and Taylor, D.*: Surv. Ophthalmol. 37:1, 1992.

Although neonatal retinal hemorrhages commonly result from birth trauma and usually resolve spontaneously without sequelae, fundus hemorrhages in infants may be important signs of ocular or systemic disorders. Hemorrhages may be associated with intracranial aneurysms, accidental or deliberate trauma, Coats' disease, persistent hyperplastic primary vitreous, retinopathy of prematurity, retinal dysplasia, hypertension, myopia, blood dyscrasias or hyperviscosity, hypotension and anoxia, cytomegalovirus or herpes simplex virus infections, carotid-cavernous sinus fistula, familial retinal arteriolar tortuosity, protein C deficiency, retinoblastoma, optic disk hamartoma, tuberous sclerosis, juvenile X-linked retinoschisis, anticoagulants, or hypercapnia. The anatomic location and appearance of fundus hemorrhages may provide important clues in the diagnosis of underlying disorders, some of which require prompt treatment to prevent amblyopia and blindness.—George B. Bartley

*The Hospitals for Sick Children, Great Ormond St., London WC1 N3JH, England.

Sinonasal primitive neuroectodermal tumor arising in a long-term survivor of heritable unilateral retinoblastoma. Klein, E. A.*, Anzil, A. P., Mezzacappa, P., Borderon, M., and Ho, V.: Cancer 70:423, 1992.

Long-term survivors of retinoblastoma are at risk to develop a second nonocular neoplasm, usually osteosarcoma in the field of radiotherapy. Such tumors nearly always develop in patients who had heritable bilateral retinoblastomas. The authors examined a woman who had been cured of a unilateral retinoblastoma after radiotherapy at 3 months of age and enucleation of the left eye at 1 year of age. Seventeen years later, epistaxis prompted a medical examination and a malignant small round cell tumor was identified in the left nasal cavity. Computed tomography showed that the mass was extensive, involving the nasal sinuses and the left frontal lobe. The patient refused further therapy until the right eye became blind three months later from massive intracranial enlargement of the neoplasm. A two-stage debulking procedure was done, but the patient died of rapid tumor regrowth within two months. Pathologic studies, including immunohistochemistry and electron microscopy, showed an undifferentiated primitive neuroectodermal tumor with early neuronal differentiation. The lesion was pathologically indistinguishable from poorly differentiated olfactory neuroblastoma and Ewing's sarcoma.—George B. Bartley

*Department of Pathology, Staten Island University Hospital, Staten Island, NY 10305.

Meningiomas are not significantly associated with breast cancer. Jacobs, D. H., Holmes, F. F.*, and McFarlane, M. J.: Arch. Neurol. 49:753, 1992.

Breast cancer and meningioma have been reported to occur in the same patient. To determine whether this association is by chance, the authors studied 283 patients with intracranial meningiomas who were treated at one institution over a 36-year period. All additional nonmeningeal malignancies and primary brain tumors were identified and the expected number of secondary tumors was calculated by a person-year method from age- and gender-matched cancer incidence data. The expected numbers of total neoplasms in the patients with meningioma and the expected tumor numbers in each major organ system were determined. Standard morbidity ratios and 95% confidence intervals were calculated for each tumor type. The number of breast cancers did not reach statistical significance. Although there was a

significantly increased number of second primary brain tumors in women and an increased number of thyroid cancers in both sexes, the authors determined that the association was notable but not conclusive.—George B. Bartley

*University of Kansas School of Medicine, 39th and Rainbow Sts., Kansas City, KS 66103.

Endocrine dysfunction in Kearns-Sayre syndrome. Harvey, J. N.*, and Barnett, D.: Clin. Endocrinol. 37:97, 1992.

Kearns-Sayre syndrome is a mitochondrial myopathy with the characteristic triad of progressive external ophthalmoplegia, pigmentary retinopathy, and cardiac conduction defects. The disease usually first manifests before the age of 20 years and may be accompanied by blepharoptosis, cerebellar dysfunction, spongiform encephalopathy, and increased cerebrospinal fluid protein concentration. Additionally, concomitant endocrine and metabolic disturbances have been described, including short stature, hypogonadism, hypoparathyroidism, diabetes mellitus, hyperaldosteronism, and hypomagnesemia. Other mitochondrial myopathy syndromes, such as "myoclonic epilepsy and ragged red fibers" and "mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes," are less likely to have associated endocrine abnormalities. The authors described a patient with all of the endocrine disorders listed previously and reviewed 226 previously published cases to determine the prevalence of these conditions. Short stature was found in 85 patients (38%), gonadal dysfunction occurred in 44 cases (19%), and diabetes mellitus was identified in 29 subjects (13%). Thyroid disease, hyperaldosteronism, and hypomagnesemia were uncommon, but may not have been sought in many cases. Although endocrine and metabolic dysfunction was found more commonly in patients with hypoparathyroidism, the authors concluded that it was probably because of increased recognition rather than increased prevalence. No evidence for an autoimmune polyendocrine syndrome was found.—George B. Bartley

*St. James University Hospital, Beckett St., Leeds LS9 7TF, United Kingdom.

Treatment of metastatic malignant melanoma with dacarbazine plus tamoxifen. Cocconi, G.*, Bella, M., Calabresi, F., Tonato, M., Canaletti, R., Boni, C., Buzzi, F., Ceci, G., Corgna, E., Costa, P., Lottici, R., Papadia, F., Sofra, M. C., and Bacchi, M.: N. Engl. J. Med. 327:516, 1992.

Dacarbazine as a single agent currently is the chemotherapy of choice for metastatic cutaneous malignant melanoma. Estrogen receptors have been identified in some melanoma specimens and positive responses to treatment of metastatic malignant melanoma with the antiestrogen drug, tamoxifen, have been reported. One hundred seventeen patients with metastatic melanoma were randomly assigned to treatment with dacarbazine alone or dacarbazine combined with tamoxifen; five patients were not included in the final data analysis because of early death, drug toxicity, or protocol violation. The overall response rate was higher (28% [17 of 60 patients] vs 12% [six of 52 patients]; P = .03) and survival was longer (median of 48 weeks vs 29 weeks; P = .02) among the patients who were treated with dacarbazine combined with tamoxifen compared with those who were treated with dacarbazine alone. There were no significant differences in response rate or survival between men and women who received dacarbazine alone. In the patients treated with dacarbazine combined with tamoxifen, however, women had better outcomes than men; the response rates were 38% (11 of 29 patients) and 19% (six of 31 patients; P = .15), respectively, and median survival was 69 weeks vs 31 weeks (P = .02), respectively. In a retrospective subgroup analysis of the patients who received dacarbazine and tamoxifen to determine indirectly the levels of endogenous estrogens, men and postmenopausal women with body-mass indices above the median value had better overall survival than those with lower body-mass indices (P < .001). The authors concluded that tamoxifen modulates chemotherapy through an estrogen-dependent mechanism and that dacarbazine in combination with tamoxifen "should now be considered standard therapy in patients with metastatic malignant melanoma."—George B. Bartley

*Medical Oncology Service, University Hospital, 43100 Parma, Italy.

Disseminated melanoma. Is there a new standard therapy? Guerry, D. IV*, and Schuchter, L. M.: N. Engl. J. Med. 327:560, 1992.

The authors of this editorial reviewed the findings of the study by Cocconi and colleagues in the same issue of the Journal; in their opinion the conclusions were "tantalizing, but premature." Melanoma is an increasingly important public health problem in the United States, where the rate of increase in the tumor's incidence (4% per year) is greater than that of any other cancer. In 1992, 32,000 new cases will be diagnosed and 6,700 deaths will be attributed to the disease. Regarding the current standard therapy of patients with disseminated melanoma, "there is none. The range of options includes simple observation of certain patients with minimal disease, surgical excision of solitary metastases, therapy with dacarbazine, participation in a clinical trial, and palliative care. Dr. Chekhov was right: 'When a lot of different remedies are suggested for a disease, that means it can't be cured.'"—George B. Bartley

*University of Pennsylvania Cancer Center, Philadelphia, PA 19104.

Basal cell carcinoma in young adults. Cox, N. H.*: Br. J. Dermatol. 127:26, 1992.

The annual incidence of basal cell carcinoma among persons aged 15 to 34 years was estimated from cancer registry data to be 37 per 100,000 total population in the northern United Kingdom during an 11-year period. Patients with the basal cell nevus syndrome were excluded. The tumor site was determined in 55 of 92 patients with sporadic basal cell carcinoma whose records were obtainable for review. The nose (13 cases), eyelids or medial canthus (ten cases), forehead (eight cases), and cheek (seven cases) were the most common regions involved. Although in larger reviews the expected frequency of a morphea histologic pattern has been shown to be 2%, this more aggressive tumor subtype was present in five patients (9%) in the current study. In addition to primary surgical or radiotherapy, 11 of 39 patients (28%) with five-year follow-up data required additional therapy for recurrence (six patients), metastasis (one patient), or a second tumor (four patients). Young adults who develop basal cell carcinoma should be considered at high risk for recurrence or secondary tumors, and diligent, long-term follow-up is appropriate.—George B. Bartley

*Department of Dermatology, Cumberland Infirmary, Carlisle CA2 7HY, United Kingdom.

Premedication for outpatient cataract surgery. A comparative study of intramuscular alfentanil, midazolam and placebo. Virkkilä, M. E. J.*, Ali-Melkkilä, T. M., and Kanto, J. H.: Acta Anaesthesiol. Scand. 36:559, 1992.

The effects of intramuscular alfentanil (a short-acting opioid analgesic) and midazolam (a benzodiazepine with a peak action 30 to 45 minutes after injection) on anxiety, sedation, hemodynamics, oxygen saturation, and intraocular pressure were compared in a double-masked, placebo-controlled study in which 90 patients who underwent outpatient cataract extraction with peribulbar anesthesia were randomly assigned to premedication. Alfentanil (12.5 μg/kg of body weight) markedly reduced anxiety (of a magnitude similar to intravenous fentanyl and sufentanil), had a short sedative effect of 30 minutes or less, and caused no hemodynamic instability. Midazolam (20 μg/kg of body weight) had a more prolonged anxiolytic and sedative effect, which caused impaired intraoperative cooperation in some patients. A significant ($P < .05$) reduction in oxygen saturation and a statistically insignificant decrease in intraocular pressure were caused by both agents. The authors concluded that alfentanil is suitable as a premedication for outpatient cataract extraction.—George B. Bartley

*Department of Anaesthesiology, University of Turku, SF-20520 Turku, Finland.

Intraoperative patient-controlled analgesia. An alternative to physician administration during outpatient monitored anesthesia care. Zelcer, J., White, P. F.*, Chester, S., Paull, J. D., and Molnar, R.: Anesth. Analg. 75:41, 1992.

Fentanyl commonly is administered for analgesia during surgical procedures that are performed with the patient under local anesthesia, but it requires three to four minutes to achieve

its maximal effect after a bolus intravenous injection, has an elimination half-life of three to six hours, and may cause ventilatory depression when given concomitantly with midazolam. The authors used a patient-controlled analgesia delivery system to assess the efficacy of alfentanil, a fast-acting and rapidly metabolized derivative of fentanyl, in comparison with conventional physician-controlled administration of alfentanil during a gynecologic procedure. The patient-controlled system had a lockout interval of three minutes. Although patients made more demands than the number of delivered bolus doses in the patient-controlled analgesia group, the total alfentanil dosage requirements and the patients' assessment of pain control were similar between the two treatment groups. Monitored vital signs, oxygen saturation, and electrocardiography showed no complications or differences between patients who administered their own analgesic and patients treated by a physician. The incidence of postoperative nausea was identical in both groups (three of 40 patients [8%] in each group).—George B. Bartley

*Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75235-9068.

The visual image in mind and brain. Zeki, S.*: Sci. Am. 267(3):68, 1992.

"The study of the visual system is a profoundly philosophical enterprise . . . our inquiry into the visual brain takes us into the very heart of humanity's inquiry into its own nature." From the late 19th century until the mid-1970s, vision was thought to result from a two-stage process: the initial creation of a retinal image or impression (similar to a photographic plate) and then decodification in the visual cortex. This "dualistic doctrine," the separation of reception from interpretation, resembles Immanuel Kant's "belief in the two faculties of sensing and of understanding, the former passive and the latter active." Research during the past two decades has refuted this hypothesis by showing that perception and comprehension occur simultaneously. Specialized functions have been correlated with different regions of the brain and four parallel systems concerned with different attributes of vision, such as color, form, and motion, have been identified. Multistage integration occurs by complex neural interconnections. The author reviewed the key historical developments in the evolution of vision research and described unusual types of acquired visual loss, such as "blindsight," "akinetopsia," and "achromatopsia," that help to explain the anatomy and function of the visual system. He concluded that understanding the visual brain requires "tackling the problem of consciousness as well," a topic that is reviewed in another article in this special issue of Scientific American devoted entirely to the mind and brain.—George B. Bartley

*Department of Neurobiology, University of London, London, England.

Should you operate on your own mother? Spaulding, W. B.*: Pharos 55(3):23, 1992.

A physician's role in the investigation or treatment of disease in a close relative is a difficult ethical issue with vague guidelines. Although making an initial diagnostic assessment or providing first aid has been considered acceptable, the ethical codes of both the American and Canadian Medical Associations have cautioned against assuming the responsibility for definitive therapy. The author argued that medical ethics, like common law, rest on the precedents of key cases, and reviewed examples from the practices of four well-known pioneering surgeons. Jose Rizal (1861–1896) performed cataract surgery on his mother; William S. Halsted (1852–1922) removed gallstones from his mother; Harvey Cushing (1869–1939) performed appendectomies on both a daughter and a son and removed a tumor from another daughter's neck; and Wilder Penfield (1891–1976) subtotally excised an extensive brain tumor in his sister. Using the patient's well-being as the ultimate standard, the author concluded that Rizal, Halsted, and Penfield honored this principle, as did Cushing in the case of the neck tumor; in each instance the surgeon's decision to treat gave the relative a better chance of a good outcome than if someone less skilled had operated. "To justify operating on a near relative, those making the decision must be convinced that no equally competent surgeon is available."—George B. Bartley

*332 Glen Manor Dr., Toronto, Ontario, Canada M4E 2X7.

NEWS ITEMS

Send News Items to
American Journal of Ophthalmology
435 N. Michigan Ave., Suite 1415
Chicago, IL 60611

The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

Ophthalmological Society of South Africa: Congress

The Ophthalmological Society of South Africa Congress will be held Feb. 14–18, 1993, in Cape Town, South Africa. For more information, write Ms. Sally Elliott, Postgraduate Medical Centre, UCT Medical School, Observatory 7925, Cape Town, South Africa; telephone (021) 47-1250 ext. 381; fax (021) 448-6263.

Aspen Corneal Society: 13th Annual Meeting

The Aspen Corneal Society will hold its 13th Annual Meeting Feb. 13–20, 1993, in Snowmass, Colorado. For further information, write Mitchell H. Friedlaender, M.D., Scripps Clinic, 10666 N. Torrey Pines Rd., La Jolla, CA 92037; telephone (619) 455-9100.

Cedars-Sinai Medical Center: Second Annual Conference on Genetic Disease of the Eye

The Cedars-Sinai Medical Genetics Birth Defects Center and the Division of Ophthalmology will sponsor the Second Annual Conference on Genetic Disease and the Eye Jan. 30, 1993, in Los Angeles, California. For more information, write Yaron S. Rabinowitz, M.D., Cornea-Genetic Eye Medical Clinic, CSMC, 444 S. San Vicente Blvd., Suite 600, Los Angeles, CA 90048; telephone (310) 855-2613.

Cleveland Clinic Foundation: Current Concepts in Ophthalmology

The Cleveland Clinic Foundation will sponsor Current Concepts in Ophthalmology Dec. 4 and 5, 1992, in Cleveland, Ohio. For more information, write Marilyn Bryce, Cleveland Clinic Educational Foundation, Dept. of Continuing Education, 9500 Euclid Ave., Room TT-31, Cleveland, OH 44195-5241; telephone (216) 444-5696 or (800) 762-8173; fax (216) 445-9406.

Contact Lens Association of Ophthalmologists: Basic Contact Lens Seminar

The Contact Lens Association of Ophthalmologists (CLAO) will sponsor Basic Contact Lens Seminar Dec. 5, 1992, at Rush Medical College in Chicago, Illinois. For further information, write Maria Patino, Cornea Service, Dept. of Ophthalmology, Rush-Presbyterian-St. Luke's Medical Center, 1725 W. Harrison St., Chicago, IL 60612; telephone (312) 942-5370.

Dana Center for Preventive Ophthalmology: Epidemiology and Preventive Ophthalmology for Ophthalmologists

The Dana Center for Preventive Ophthalmology, Wilmer Institute, Johns Hopkins University School of Medicine, will offer its one-year course, Epidemiology and Preventive Ophthalmology for Ophthalmologists, beginning July 1, 1993. For additional information, write Sheila West, Ph.D., PHO Admissions Committee, Dana Center, Wilmer 116, Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21205; telephone (410) 955-2777; fax (410) 955-2542.

Edward S. Harkness Eye Institute: Cadaver Dissection of the Lid and Orbit

The Edward S. Harkness Eye Institute of Columbia-Presbyterian Medical Center will sponsor a hands-on course, Cadaver Dissection of the Lid and Orbit, Jan. 26 and 27, 1993. For additional information, write John C. Merriam, M.D., Edward S. Harkness Eye Institute, 635 W. 165th St., New York, NY 10032; telephone (212) 305-5402.

New York Eye and Ear Infirmary: Advanced Phacoemulsification and Foldable Intraocular Lens Implantation and Keratorefractive Surgery Course

The New York Eye and Ear Infirmary will sponsor a course, Advanced Phacoemulsification and Foldable Intraocular Lens Implantation and Keratorefractive Surgery, April 30 and May 1, 1993, in New York, New York. For more information, write Sylvia Sorrentino, Institute for Continuing Medical Education, New York Eye and Ear Infirmary, Second Ave. & 14th St., New York, NY 10003; telephone (212) 979-4430 or (212) 979-4444; fax (212) 979-4441.

Prentice Eye Institute: 19th Annual Frontiers in Ophthalmology

The Prentice Eye Institute of St. Luke's Medical Center will hold its 19th Annual Frontier in Ophthalmology Feb. 25–27, 1993, at Red Lion's La Posada Resort, Scottsdale, Arizona. For additional information, write Frontiers in Ophthalmology, St. Luke's Medical Center, 1800 E. Van Buren, Phoenix, AZ 95006; telephone (602) 251-8590.

Retina Research Conference: Advanced Retina Symposium

The Retina Research Conference will sponsor Advanced Retina Symposium March 19 and 20, 1993, in San Francisco, California. For more information, write Lorraine Geary, Retina Research Conference, P.O. Box 640370, San Francisco, CA 94164; telephone (415) 441-1057.

Wilmer Ophthalmological Institute: 10th Annual Current Concepts in Ophthalmology

The Wilmer Ophthalmological Institute of the Johns Hopkins Medical Institutions will sponsor the 10th Annual Current Concepts in Ophthalmology with phacoemulsification wet lab and vitrectomy workshop for the anterior segment surgeon March 14–19, 1993, in Vail, Colorado. For additional information, write the Program Coordinator, Johns Hopkins Medical Institutions, Office of Continuing Education, Turner Bldg., 720 Rutland Ave., Baltimore, MD 21205-2195; telephone (410) 955-2959.

Wilmer Ophthalmological Institute: 1993 Update in the Management of Age-related Macular Degeneration

The Wilmer Ophthalmological Institute of the Johns Hopkins Medical Institutions will sponsor the 1993 Update in the Management of Age-related Macular Degeneration with an optional fluorescein angiography workshop Jan. 22 and 23, 1993, in Baltimore, Maryland. For more information, write the Program Coordinator, Johns Hopkins Medical Institutions, Office of Continuing Education, Turner 20, 720 Rutland Ave., Baltimore, MD 21205; telephone (410) 955-2959; fax (410) 955-0807.

Dallas Academy of Ophthalmology: 1993 Officers

The Dallas Academy of Ophthalmology has elected the following officers for 1993: William L. Hutton, president; Thomas P. Hawk, vice president and public education committee chairman; Rand Spencer, secretary-treasurer; and Ronald Fellman, program chairman.

Kentucky Academy of Eye Physicians and Surgeons: 1993 Officers

The Kentucky Academy of Eye Physicians and Surgeons has elected the following officers for 1993 Richard A. Eiferman, president; Bruce Koffler, president elect; Richard A. Bowers, secretary-treasurer; and M. Douglas Gossman, chairman, Third Party Committee.

Research to Prevent Blindness: Senior Scientific Investigator Awards

Research to Prevent Blindness has granted Senior Scientific Investigator Awards in the amount of $45,000 each to ten nationally recognized senior scientists conducting eye research at medical institutions in the United States. The 1992 Research to Prevent Blindness Senior Scientific Investigator Awards were given to the following investigators: Ted S. Acott, Ph.D., Oregon Health Sciences University; Ruben Adler, M.D., Johns Hopkins University; Janice M. Burke, Ph.D., Medical College of Wisconsin;

Anita E. Hendrickson, Ph.D., University of Washington; Joseph Horwitz, Ph.D., University of California, Los Angeles; Chris A. Johnson, Ph.D., University of California, Davis; Thomas Mittag, Ph.D., Mount Sinai School of Medicine; Jerry Y. Niederkorn, Ph.D., University of Texas Southwestern, Dallas; Narsing A. Rao, M.D., University of Southern California; and Harris Ripps, Ph.D., University of Illinois, Chicago.

Fight for Sight: 1992 Eye and Vision Research Grants

The National Society to Prevent Blindness Fight For Sight Research Division recently awarded more than $400,000 in grants to 50 different awardees to fight blindness through medical and vision research.

Postdoctoral Fellowships

Michael L. Cooper, Ph.D., M.D., Mt. Sinai Medical School, New York, NY (Steven M. Podos, M.D., Sponsor). Ocular Blood Flow in Glaucoma. (Awarded in Memory of Mary E. and Alexander P. Hirsch.)

Mordechai Goldenfeld, M.D., Northwestern University, Chicago, IL (Jon M. Ruderman, M.D., Sponsor). Optic Disc Analysis Using Digitized Photography and Flicker Analysis.

Karen L. Kittredge, M.D., University of Virginia, Charlottesville, VA (Federico Gonzalez-Fernandez, Ph.D., Sponsor). Molecular & Functional Analysis of Interphotoreceptor Retinol-Binding Protein (RBP) in Xenopus Laevis.

Ioannis Koutalos, Ph.D., Johns Hopkins University, Baltimore, MD (King-Wai Yau, Ph.D., Sponsor). Phototransduction in Retinal Cone Cells. (Awarded in Memory of Mary E. and Alexander P. Hirsch.)

Ilona Kovacs, Ph.D., Rutgers University, New Brunswick, NJ (Bela Julesz, Ph.D., Sponsor). Learning Effects & Interaction of Different Visual Attributes in Stereoscopic Depth Perception. (Awarded in Memory of Dr. Hermann M. and Gladys Burian.)

Elsa M. Raskin, M.D., New York Eye & Ear Infirmary, New York, NY (Mark G. Speaker, M.D., Ph.D., Sponsor). Molecular Biology of Staphylococci Causing Postoperative Endophthalmitis. (Awarded in Tribute to Bob Hope.)

Ellie E. Samadani, M.D., Wayne State University, Detroit, MI (Robert N. Frank, M.D., Sponsor). Studies of the Physiology and Pathophysiology of the Retinal Capillaries. (Awarded in Honor of Dr. Charles A. Perera.)

Elcio H. Sato, M.D., Eye Research Institute, Boston, MA (David A. Sullivan, Ph.D., Sponsor). Influence of Hormone Therapy in Sjogren's Syndrome in Lacrimal Gland.

Andrew W. Taylor, Ph.D., University of Miami, Miami, FL (Scott W. Cousins, M.D., Sponsor). Immunosuppressive Activity of a-MSH in Aqueous Humor.

Lifang Tien, M.D., Ph.D., Baylor College of Medicine, Houston, TX (Joe G. Hollyfield, Ph.D., Sponsor). The Composition and Cellular Origin of the WGA-Binding Domain of the IPM in the Human Retina.

Grants-in-Aid

Thomas J. Beyers, Ph.D., Ohio State University, Columbus, OH. Ribosomal RNA and DNA Sequence Discrepancies in Acanthamoeba.

Mark H. Criswell, Ph.D., Chicago Medical School, North Chicago, IL. Rabbit Starburst Amacrine Cells: A Study to Correlate Structure with Function.

Elizabeth A. Debski, Ph.D., University of Kentucky, Lexington, KY. Somatostatin, VIP and Visual Map Formation in Rana Pipiens.

Michael A. Edwards, Ph.D., Eunice Kennedy Shriver Center, Waltham, MA. Defective Optic Axon Outgrowth in an Anophthalmic Mutant Mouse: Analysis Using Chimeras and Immunocytochemistry.

Felix I. Ifeanyi, Ph.D., Kansas State University, Manhattan, KS. Identification of Lens Membrane Recognition Site(s) of Alpha Crystallin.

Terence P. Ma, Ph.D., University of Mississippi Medical Center, Jackson, MS. Functional Relationship of the Incertotectal Projection in the Macaque.

Steven A. Madreperla, M.D., Ph.D., Johns Hopkins University, Baltimore, MD. Replacement of the RB Gene in Retinoblastoma Cells: Effects on Tumorigenesis. (Awarded in Tribute to Bob Hope.)

Helen McIntosh, Ph.D., Washington University, St. Louis, MO. Localization and Biochemical Characterization of Adenosine A2 Receptors in Bovine Rod Outer Segments.

Jay F. Muller, Ph.D., Washington University, St. Louis, MO. Synaptic Connectivity of Transplanted Photoreceptors.

Ramesh C. Nayak, Ph.D., Joslin Diabetes Center, Boston, MA. Characterization of Retinal Microvascular Pericyte Antigens Defined by Circulating Anti-Pericyte Antibodies in Reti-

nopathic Diabetes. (Awarded in Memory of Mary E. and Alexander P. Hirsch.)

Ann M. Repka, Ph.D., Johns Hopkins University, Baltimore, MD. Investigation Into the Factors Controlling the Determination of Retinal Precursor Cell Phenotype.

Bratin K. Saha, Ph.D., Washington University, St. Louis, MO. Development of Novel RFLP Probes for Carrier Detection and Prenatal Diagnosis of X-Linked Retinitis Pigmentosa. (Awarded in Memory of Silas Adelsheim.)

Ursula M. Schmidt, M.D., Massachusetts General Hospital, Boston, MA. Carrier Systems for Improved Selectivity of Photodynamic Therapy in Vascular Occlusion.

Marc D. Servetnick, Ph.D., University of Virginia, Charlottesville, VA. Regulation of Competence for Lens Induction in Xenopus Development.

Carol B. Toris, Ph.D., University of Nebraska, Omaha, NE. Mechanism of Action of Acetazolamide Decreasing Intraocular Pressure.

Janey L. Wiggs, M.D., Ph.D., Massachusetts Eye & Ear Infirmary, Boston, MA. Genetic Linkage Study of Autosomal Dominant Juvenile Glaucoma.

Steven E. Wilson, M.D., University of Texas, Dallas, TX. Growth Factor and Growth Factor Receptor mRNA Expression in Corneal Epithelium.

Tanweer S. Zaidi, Ph.D., Tufts University, Boston, MA. The Role of Ocular Mucus in Providing Protection From Pseudomonal Corneal Infection.

Student Fellowships

Jameel Almed, Northwestern University, Evanston, IL (Robert A. Linsenmeier, Ph.D., Sponsor). Regional Variations in Oxygen Supply and Photoreceptor Oxygen Consumption in the Cat Retina. (Awarded in Memory of Herman Shane.)

Claire L. Bautista, University of South Florida, Tampa, FL (Alvin F. Wells, Ph.D., Sponsor). The Role of Borrelia Antigens in Ocular Inflammation. (Awarded in Honor of Neil and Donna Weisman.)

Anastasia V. Deliganis, University of Washington, Seattle, WA (Thomas A. Reh, Ph.D., Sponsor). Basic Fibroblast Growth Factor Receptor Expression During Retinal Regeneration. (Supported by The Albert G. and Herman B. Mosler Memorial Fund.)

Karen V. Gonzalez, Kansas State University, Manhattan, KS (Dolores J. Takemoto, Ph.D., Sponsor). The Role of the Na+, K+ −ATPase in Diabetic Retinopathy and Cataract Formation. (Supported by a grant from the Radio and Television Square Club.)

Terry Kim, Duke University, Durham, NC (Gordon K. Klintworth, M.D., Ph.D., Sponsor). Investigation of the Effects of Vasoconstriction on Corneal Neovascularization Using an In Vivo Model. (Awarded in Memory of Norma Cohen.)

E. Anders Kolb, University of Pennsylvania, Philadelphia, PA (David J. Calkins, Ph.D., Sponsor). The Microcircuitry of the Midget Ganglion Cell Pathway in Macaca.

Norman L. Lehman, Jr., University of California, San Francisco, CA (Richard B. Crook, Ph.D., Sponsor). Na+, K+, Cl− Cotransport in Postnatal Human Non-Pigmented Ciliary Epithelial Cells. (Awarded in Honor of Elsie K. Sloate.)

Bettye D. Ridley, University of Kentucky, Lexington, KY (Philip H. Bonner, Ph.D., Sponsor). The Development of Extraocular Muscle in Chick Embryos. (Awarded in Memory of Selma Rabin.)

Keith Rosol, Wayne State University, Detroit, MI (Linda D. Hazlett, Ph.D., Sponsor). Localization of Putative Host Receptors for *P. Aeruginosa* in the Mouse Eye. (Awarded in Memory of Selma Rabin.)

Isaac E. Silverman, Princeton University, Princeton, NJ (Charles G. Gross, Ph.D., Sponsor). Visual Imagery in the Macaque: Lesion & Electrophysiological Investigations.

Peter L. Sonkin, Duke Eye Center, Durham, NC (Diane L. Hatchell, Ph.D., Sponsor). The In Vivo Effects of Pentoxifylline on the Deformability of PMNs in a Cat Model of Diabetes. (Supported by the James Thurber Memorial Fund.)

Catherine D. Thaler, University of California, Riverside, CA (Leah T. Haimo, Ph.D., Sponsor). Regulation of Organelle Transport in RPE. (Supported by the James Thurber Memorial Fund.)

Jingjing Ye, New York University, New York, NY (Jose A. Zadunaisky, M.D., Ph.D., Sponsor). Membrane Transport and H2O2 Oxidating Efin Lens Epithelial and Fiber Cell Membrane Vesicles. (Supported by a grant from Canon, USA, Inc.)

J. Arch McNamara, M.D., Wills Eye Hospital,

Philadelphia, PA. Laser Photocoagulation for Stage 3+ Retinopathy of Prematurity.

Personals

George B. Bartley

George B. Bartley has been appointed chairman of the Department of Ophthalmology at the Mayo Clinic in Rochester, Minnesota. He succeeds Richard F. Brubaker, who served from 1984 until October 1992. Previous chairs include William L. Benedict (1917–1949), C. Wilbur Rucker (1949–1961), John W. Henderson (1961–1974), and Robert R. Waller (1974–1984). Dr. Bartley is a graduate of Miami University in 1978 and the Ohio State University College of Medicine in 1981. He completed an internship in Columbus, served his residency at the Mayo Clinic from 1982 to 1985, and received subspecialty training in oculoplastic and orbital surgery from John D. Bullock. Dr. Bartley is the current Abstract Editor for THE AMERICAN JOURNAL OF OPHTHALMOLOGY.

Edward B. Feinberg
Randall L. Funderburk

Edward B. Feinberg and Randall L. Funderburk of Retina Associates, Chattanooga, Tennessee, are the recipients of the Melvin Jones Fellow Award from the Lions Club International Foundation. The Melvin Jones Fellowship is symbolized by such attributes as generosity, compassion, and concern for others. The award is the highest commendation conferred by the Lions Clubs International Foundation for humanitarian service.

Denis M. O'Day

Denis M. O'Day has been named chairman of the Department of Ophthalmology at Vanderbilt University Medical Center, Nashville, Tennessee.

Racial Differences in the Prevalence of Intraocular Lens Implants in the United States

Catherine M. Sharkness, M.D., Stanford Hamburger, D.D.S., Ronald G. Kaczmarek, M.D., Peggy M. Hamilton, B.S., Roselie A. Bright, Sc.D., and Roscoe M. Moore, Jr., D.V.M.

We generated population-based estimates of the prevalence of intraocular lens implants by using the 1988 Medical Device Implant Supplement to the National Health Interview Survey. This national survey of a probability sample of the civilian noninstitutionalized United States population comprised 47,485 households and 122,310 persons. To produce national projections, we used survey respondent-reported data based on 1,941 reported intraocular lenses in 1,337 persons.

Projected to the United States population, an estimated 2.6 million people had a total of 3.8 million lens implants. The predominant reason for the implant was cataract. The intraocular lens replacement rate was 0.9%. The use of intraocular lens implants was statistically significantly different from the general population in persons with the following socioeconomic characteristics: age (65 years or older), race (white), gender (female), annual family income (less than $20,000, although more commonly at or above the poverty threshold), and education (less than high school). The prevalence rates per 1,000 persons according to age were as follows: 0.3 for persons 44 years old or younger, 9.9 for persons 45 to 64 years old, 33.3 for persons aged 65 to 69 years, 63.5 for persons aged 70 to 74 years, and 113.5 for persons 75 years old or older. Additionally, prevalence rates according to socioeconomic factors were as follows: 12.1 for whites and 3.3 for nonwhites, 12.9 for females and 8.4 for males, 18.2 for persons with a family income less than $20,000 and 6.7 for persons with a family income of $20,000 or more, 10.5 for persons above the poverty threshold and 8.0 for persons below the poverty threshold, and 13.2 for persons with less than 12 years of education and 10.7 for persons with at least 12 years of education. The racial difference remained after controlling for the effects of age. The underuse of intraocular lenses among nonwhites warrants further investigation, given the improvement in vision that results from cataract extraction with implantation of an intraocular lens.

CATARACTS are a major, but correctable, cause of blindness in the United States. About 97% of cataract operations in the United States involve intraocular lenses. Intraocular lenses offer a superior visual result compared with the use of cataract spectacles after cataract removal. The result is superior because image magnification and spatial distortion are eliminated. Also, with the use of intraocular lenses after cataract extraction, peripheral vision is not restricted.[1] The use of intraocular lenses allows the removal of a cataract in one eye while still preserving binocular vision.[2] Given the greatly improved functional status attributable to visual rehabilitation afforded by the use of intraocular lenses,[3] it is not surprising that cataract extraction is currently the most frequently performed surgical procedure reimbursed by Medicare.[4]

We studied population-based estimates of the prevalence of intraocular lens use in the United States, and compared socioeconomic characteristics of the recipients with those of the general population. Age-adjusted comparisons were performed, as well as an analysis by number of implants.

Accepted for publication Sept. 25, 1992.

From the Center for Devices and Radiological Health, United States Food and Drug Administration, Rockville, Maryland (Drs. Sharkness, Hamburger, Kaczmarek, and Bright and Ms. Hamilton); and Office of International Health, Office of the Assistant Secretary for Health, Rockville, Maryland (Dr. Moore).

Reprint requests to Ronald G. Kaczmarek, M.D., FDA/CDRH, 5600 Fishers Ln., HFZ-161, Rockville, MD 20857.

TABLE 1
NUMBER AND PREVALENCE RATE OF INTRAOCULAR LENSES BY SOCIODEMOGRAPHIC CHARACTERISTICS*

SOCIODEMOGRAPHIC CHARACTERISTIC	PERSONS WITH IMPLANTS (N = 2,582) (THOUSANDS)	ALL PERSONS (N = 240,890) (THOUSANDS)	PREVALENCE RATE (PER THOUSAND)	95% CONFIDENCE INTERVAL
Age (yrs)†‡				
≤ 44	49	166,634	0.3	0.1, 0.5
45–64	453	45,573	9.9	8.1, 11.7
65–69	326	9,801	33.3	26.3, 40.3
70–74	493	7,764	63.5	52.9, 74.1
75–99	1,262	11,118	113.5	102.1, 124.9
Race†				
White	2,457	203,256	12.1	11.1, 13.1
Nonwhite	125	37,634	3.3	2.1, 4.5
Gender†				
Female	1,599	124,232	12.9	11.7, 14.1
Male	983	116,657	8.4	7.4, 9.4
Region†§				
Midwest	709	59,543	11.9	10.3, 13.5
South	918	82,278	11.2	9.8, 12.6
West	490	49,797	9.8	8.2, 11.4
Northeast	466	49,271	9.5	7.9, 11.1
Metropolitan statistical area residence†‖				
Central city	780	74,860	10.4	9.0, 11.8
Not central city	1,036	111,362	9.3	8.1, 10.5
Not a resident of a metropolitan statistical area	746	54,668	13.6	11.6, 15.6
Family income (dollars)†				
< 20,000	1,504	82,736	18.2	16.4, 20.0
≥ 20,000	1,007	151,204	6.7	5.9, 7.5
Poverty status†				
Not in poverty	2,048	195,466	10.5	9.7, 11.3
In poverty	208	26,017	8.0	5.8, 10.2
Education†				
< 12 years	1,104	83,473	13.2	11.6, 14.8
≥ 12 years	1,459	136,587	10.7	9.7, 11.7

*Totals may not equal 100% because of missing or rounded values; includes unknown family income, poverty status, and education.

†Stratum-specific prevalence rates are statistically significantly different from each other at the .05 level.

‡Age comparisons are between 44 years or younger and 45 to 64 years, 45 to 64 years and 65 to 69 years, 65 to 69 years and 70 to 74 years, 70 to 74 years and 75 to 99 years.

§A significant difference in rates was found for a comparison between Northeast and Midwest. No significant differences were found for Northeast and South or Northeast and West.

‖A significant difference in rates was found for a comparison between central city part of a metropolitan statistical area and nonmetropolitan statistical area. No significant difference was found for central city part of a metropolitan statistical area and noncentral city part of a metropolitan statistical area.

TABLE 2
AGE-SPECIFIC RATES OF INTRAOCULAR LENS USE BY RACE

AGE (YRS)	WHITES PREVALENCE RATE (PER THOUSAND)	WHITES 95% CONFIDENCE INTERVAL	NONWHITES PREVALENCE RATE (PER THOUSAND)	NONWHITES 95% CONFIDENCE INTERVAL	P VALUE
< 65	2.7	2.3, 3.1	0.8	0.2, 1.4	P < .05
65–72	44.1	37.4, 50.8	23.8	9.5, 38.1	P < .05
73–79	92.6	80.3, 105.0	36.5	11.6, 61.4	P < .05
80–99	138.6	120.4, 156.8	63.0	22.0, 104.0	P < .05

Methods

The National Health Interview Survey is a continuing, cross-sectional household interview survey that has been conducted by the National Center for Health Statistics each year since 1957. This survey is the principal source of information about the health of the United States population. Each year, basic health and sociodemographic information is collected on a probability sample of the civilian, noninstitutionalized population of the United States in home interviews conducted by Bureau of the Census personnel. Additionally, detailed information on selected health topics is included by using supplemental questionnaires.

As part of the 1988 National Health Interview Survey, the Medical Device Implant Supplement was implemented and conducted by the Food and Drug Administration's Center for Devices and Radiological Health and the National Center for Health Statistics. The Medical Device Implant Supplement was designed to generate the first population-based estimates of the prevalence of selected generic types of medical device implants. The questionnaire used in this supplement contained a screening section and six sections dealing with the following devices: artificial joints, fixation devices, artificial heart valves, pacemakers, intraocular lenses, and other types of implanted devices. The screening section identified household members who currently had an implant. Specific questions were then asked of each family member who had an implant. Questions about replacement, duration of use, and morbidity were included. All data were obtained by questionnaire and medical records were not consulted. The response rate was 92%.[5]

We restricted our study to intraocular lens implants. Our estimates are based on the survey sample, which was weighted to produce national estimates. The weighting process accounted for the survey design and adjusted for nonresponse. Approximate standard errors, 95% confidence intervals of the estimated rates, and P values were computed by using a standard published procedure.[5,6] Statistical significance was assessed at the .05 level. Itemized totals may not equal 100% because of rounding error or missing data.

The demographic terms used in this study were the same as those used in the National Health Interview Survey.[6] The age reported was

TABLE 3
AGE-SPECIFIC RATES OF INTRAOCULAR LENS USE BY EDUCATIONAL LEVEL

AGE (YRS)	NO HIGH SCHOOL DIPLOMA PREVALENCE RATE (PER THOUSAND)	NO HIGH SCHOOL DIPLOMA 95% CONFIDENCE INTERVAL	HIGH SCHOOL DIPLOMA OR BETTER PREVALENCE RATE (PER THOUSAND)	HIGH SCHOOL DIPLOMA OR BETTER 95% CONFIDENCE INTERVAL	P VALUE
< 65	1.8	1.2, 2.4	2.8	2.2, 2.8	P < .05
65–74	43.9	33.5, 54.3	41.3	33.5, 49.1	P > .05
73–79	79.6	63.7, 95.5	96.8	79.9, 113.7	P > .05
80–99	121.2	99.6, 142.8	151.8	122.8, 180.8	P > .05

TABLE 4
AGE-SPECIFIC RATES OF INTRAOCULAR LENS USE BY POVERTY LEVEL

AGE (YRS)	NOT IN POVERTY PREVALENCE RATE (PER THOUSAND)	NOT IN POVERTY 95% CONFIDENCE INTERVAL	IN POVERTY PREVALENCE RATE (PER THOUSAND)	IN POVERTY 95% CONFIDENCE INTERVAL	P VALUE
< 65	2.4	2.0, 2.8	1.7	0.7, 2.7	P > .05
65–74	42.0	35.1, 48.9	58.7	30.1, 87.3	P > .05
73–79	95.3	81.6, 109.0	84.6	46.0, 123.2	P > .05
80–99	143.9	122.3, 165.5	87.1	44.0, 130.2	P < .05

the age at the last birthday. For geographic region, the United States was divided into the following four regions: Northeast, Midwest, South, and West. Residence was classified as inside or outside a metropolitan statistical area, which was defined as follows: a county or group of counties that contained at least one city with a population of 50,000 or more, and adjacent counties (which may cross state lines) that were metropolitan in character and were economically and socially integrated with the central city. In New England, towns and cities rather than counties were the units used in defining metropolitan statistical areas.[6] The poverty level was defined by family size, number of children, and family income according to 1987 poverty levels defined by the United States Bureau of the Census.[5]

Results

Device estimates—Among survey respondents, 1,941 lens implants were reported. Projected to the United States population, an estimated 3.8 million (95% confidence interval, 3.6 to 4.0 million) lenses were in use in 1988. Reasons for the implant included (not mutually exclusive) cataract in 94.4% of the lens implants (3.6 million), injury in 0.7% of the lens implants (26,000), and other unspecified reasons in 4.4% of the lens implants (166,000). The lens implants were bilateral in 63% of the cases (2.4 million) and unilateral in 37% of the cases (1.4 million). The site of the implant was the right eye in 52% of the lens implants (2.0 million) and the left eye in 47% of the lens implants (1.8 million). The mean duration of use of the implant was 3.1 years, with a range of less than six months to 24 years. Thirty percent of implants (1.1 million) were used for one year or less, 48.5% (1.8 million) for two to five years, 14% (524,000) for more than five years, and 8% (282,000) had an unknown duration of use. Finally, the current lens was a replacement in 0.9% of the lens implants (35,000).

Person estimates—In the survey, 1,337 persons reported at least one lens implant. Projected to the United States population, an estimated 2.6 million (95% confidence interval, 2.4 to 2.8 million) people had intraocular lenses. The mean age was 73 years (range, 2 to 99 years).

Sociodemographic characteristics of persons

TABLE 5
AGE-SPECIFIC RATES OF INTRAOCULAR LENS USE BY REGION OF COUNTRY

AGE (YRS)	NORTHEAST* PREVALENCE RATE (PER THOUSAND)	NORTHEAST* 95% CONFIDENCE INTERVAL	MIDWEST PREVALENCE RATE (PER THOUSAND)	MIDWEST 95% CONFIDENCE INTERVAL	P VALUE	SOUTH PREVALENCE RATE (PER THOUSAND)	SOUTH 95% CONFIDENCE INTERVAL	P VALUE
< 65	2.0	1.2, 2.8	2.4	1.6, 3.2	P > .05	2.7	1.9, 3.5	P > .05
65–72	31.2	20.0, 42.4	47.6	34.1, 61.1	P > .05	41.8	31.2, 52.4	P > .05
73–79	63.8	42.6, 85.0	103.0	78.3, 127.7	P < .05	83.4	64.4, 102.4	P > .05
80–99	117.2	84.1, 150.3	146.7	110.8, 182.6	P > .05	141.8	111.6, 172.0	P > .05

*The statistical comparisons are between the Northeast and each of the other three regions.

with intraocular lenses were compared to all persons in the United States (Table 1). As expected, prevalence rates increased significantly with age: 0.3 persons per 1,000 had lens implants among persons 45 years old or younger, compared to 113.5 persons per 1,000 with lens implants among persons 75 years old or older. Prevalence rates were significantly higher in those who were white and female, in those with a lower family income (although this income was more commonly at or above the poverty threshold), and in those with less than a high-school education. The low family income reflected the older age of the intraocular lens recipients who were no longer receiving a salary. Some differences in rates of use of intraocular lenses were found for region of country and residence in a metropolitan statistical area. A significant difference in rates was found for a comparison between Northeast and Midwest, whereas no significant differences were found for Northeast vs South or Northeast vs West. A significant difference in rates was found for a comparison between residence in the central part (city) of a metropolitan statistical area and residence in a nonmetropolitan statistical area, whereas no significant difference was found for residence in the central part (city) of a metropolitan statistical area and residence in the noncentral part (outside the city) of a metropolitan statistical area.

Sociodemographic characteristics (age, race, gender, income, poverty status, education, residence in a metropolitan statistical area, and region of the country) of persons with one vs two implants did not differ significantly in any comparison.

Age-stratified analyses—Because of the differing age distributions of intraocular lens recipients and the general population, age adjustment was performed to control for the confounding effect of age. By this method, the association of the characteristic of interest independent of age could be assessed.[7]

Rates of intraocular lens use in recipients younger than 65 years compared to those who were older were examined, by evaluating sociodemographic characteristics (Tables 2 through 8). Significantly higher prevalence rates for whites compared to nonwhites persisted after age stratification (Table 2). The differences in prevalence rates by race were greatest in the youngest age stratum: the prevalence ratio of intraocular lens use in whites was more than three times that in blacks for those younger than 65 years. The prevalence ratio for whites compared to blacks was 1.9 for 65- to 72-year-olds, 2.5 for 73- to 79-year-olds, and 2.2 for people 80 years old or older.

After age stratification, some differences remained for the following three characteristics: education, poverty status, and region of country. Among those younger than 65 years, a higher rate of intraocular lens use was found in persons with at least a high-school education, compared to those with less than a high-school education (Table 3). A higher rate of intraocular lens use was found in 80- to 99-year-olds who were not in poverty compared to those who were in poverty (Table 4). Finally, regional differences were found in the 73- to 79-year-olds for comparisons between the Northeast and the Midwest and West (Table 5).

No statistically significant differences in rates after age stratification were apparent for the following: gender (Table 6), income (Table 7), and residence in a metropolitan statistical area (Table 8).

TABLE 5 *(continued)*
AGE-SPECIFIC RATES OF INTRAOCULAR LENS USE BY REGION OF COUNTRY

	WEST		
AGE (YRS)	PREVALENCE RATE (PER THOUSAND)	95% CONFIDENCE INTERVAL	P VALUE
< 65	2.2	1.4, 3.0	P > .05
65–72	48.1	33.0, 63.2	P > .05
73–79	101.5	72.7, 130.3	P < .05
80–99	111.1	72.7, 149.5	P > .05

Discussion

Because most cataract operations involve the use of intraocular lenses, prevalence information about such implants is needed for both clinicians and public health workers in the vision care field. To date, estimates about intraocular lenses have been supplied by manufacturers and have been based on sales data, which do not necessarily reflect the number of devices actually implanted. Although the number and type of intraocular lenses are reported, the historical information about the recipients needed to generate population-based estimates

TABLE 6
AGE-SPECIFIC RATES OF INTRAOCULAR LENS USE BY GENDER

AGE (YRS)	MALES PREVALENCE RATE (PER THOUSAND)	MALES 95% CONFIDENCE INTERVAL	FEMALES PREVALENCE RATE (PER THOUSAND)	FEMALES 95% CONFIDENCE INTERVAL	P VALUE
< 65	2.3	1.7, 2.9	2.5	1.9, 3.1	P > .05
65–72	36.8	28.0, 45.6	45.9	37.3, 54.5	P > .05
73–79	80.6	63.4, 97.8	92.0	76.7, 107.3	P > .05
80–99	119.7	91.7, 147.7	138.1	116.7, 159.5	P > .05

are lacking.[5] Data from restricted patient populations, such as surgical series or surgical case reports, which are not population based, are subject to selection bias. The 1988 Medical Device Implant Supplement to the National Health Survey overcomes the previously mentioned problems because it is population based and contains information about the recipients of the lens implants.

Rates of intraocular lens prevalence increased significantly with age. This increase mirrors the increasing prevalence of cataracts (the most common reason for surgery) with increasing age. In the Framingham study,[8] 18% of persons aged 65 to 74 years had cataracts that reduced visual acuity to 20/30 or worse compared to 46% for persons aged 75 to 84 years. Age effects accounted for most of the differences in rates of intraocular lens use for the evaluated sociodemographic characteristics.

Our most important finding was the racial variation in intraocular lens prevalence. The underrepresentation of nonwhites with intraocular lenses was observed for the elderly intraocular lens recipients (those at least 65 years old) and the nonelderly intraocular lens recipients (those younger than 65 years). However, the degree of underrepresentation for nonelderly intraocular lens recipients was greater than for the elderly intraocular lens recipients, which questions the access of nonwhites to intraocular lenses in those not old enough to be eligible for Medicare. Surveys of physicians have indicated that physicians are more willing to accept Medicare patients than Medicaid patients,[9] which is consistent with the existence of an access problem in those younger than 65 years.

Assuming the incidence of cataracts in white and nonwhite patients and the use of intraocular lenses in white and nonwhite patients undergoing cataract extraction are equal, the racial differences in the prevalence of intraocular lenses are curious. The following recent studies provide information on race, visual impairment, and cataract extraction that may help to explain the reasons for the racial variation in use of intraocular lenses.

In the Baltimore Eye Survey,[10] race was associated with low visual acuity. Blacks had an age-adjusted twofold increased prevalence of blindness and visual impairment compared to whites, irrespective of the definition of impairment. The relative prevalence for blacks compared to whites was 2.1 for visual impairment and 2.4 for blindness. After adjustment for the socioeconomic variables of educational level,

TABLE 7
AGE-SPECIFIC RATES OF INTRAOCULAR LENS USE BY FAMILY INCOME

AGE (YRS)	INCOME < $20,000 PREVALENCE RATE (PER THOUSAND)	INCOME < $20,000 95% CONFIDENCE INTERVAL	INCOME ≥ $20,000 PREVALENCE RATE (PER THOUSAND)	INCOME ≥ $20,000 95% CONFIDENCE INTERVAL	P VALUE
< 65	2.9	2.1, 3.7	2.2	1.8, 2.6	P > .05
65–72	45.0	36.2, 53.8	40.1	30.9, 49.3	P > .05
73–79	87.4	73.1, 101.7	93.0	72.0, 114.0	P > .05
80–99	125.9	105.9, 145.9	147.5	111.8, 183.2	P > .05

TABLE 8
AGE-SPECIFIC RATES OF INTRAOCULAR LENS USE BY RESIDENCE IN A METROPOLITAN STATISTICAL AREA*

AGE (YRS)	METROPOLITAN STATISTICAL AREA CENTRAL CITY PREVALENCE RATE (PER THOUSAND)	95% CONFIDENCE INTERVAL	METROPOLITAN STATISTICAL AREA NOT CENTRAL CITY PREVALENCE RATE (PER THOUSAND)	95% CONFIDENCE INTERVAL	P VALUE	NONMETROPOLITAN STATISTICAL AREA PREVALENCE RATE (PER THOUSAND)	95% CONFIDENCE INTERVAL	P VALUE
< 65	2.3	1.5, 3.1	2.4	1.8, 3.0	P > .05	2.5	1.7, 3.3	P > .05
65–74	37.4	26.8, 48.0	41.8	32.4, 51.2	P > .05	47.3	34.4, 60.2	P > .05
73–79	84.9	64.5, 105.3	80.0	62.8, 97.3	P > .05	100.4	77.5, 123.3	P > .05
80–99	137.7	107.9, 167.5	119.9	93.6, 146.2	P > .05	141.7	107.8, 175.6	P > .05

*Comparison is between the central city part of the metropolitan statistical area and each of the other two areas.

employment, and general health status, however, the relative prevalence was reduced to between 1.2 and 1.4 for visual impairment and blindness, respectively. This indicates that blacks may not be predisposed to a higher risk of low visual acuity, but that other factors associated with loss in visual acuity are also associated with race in the population studied.[11]

Using 1986 to 1987 Medicare data, the Patient Outcomes Research Team study[12] on cataract extraction found rates of cataract extraction for whites were significantly higher than for blacks. In this preliminary analysis, the ratio for whites was 1.4 times that for blacks in 1986 and 1.25 times that for blacks in 1987, with the differences persistent across all census divisions and almost all states.

In another study by the Baltimore Eye Survey,[13] age-related cataract for which no operation was performed was the leading cause of blindness among blacks, accounting for almost one third of all blindness in that group. Age-adjusted rates of age-related cataract were over five times greater among blacks than among whites. Also, whites were almost 50% more likely than blacks to have undergone cataract extraction before 80 years of age ($P < .002$). The authors concluded that the high rate of unoperated cataract in younger blacks and the elderly of both races suggests underutilization of health services. Thus, the finding of greater use of intraocular lenses by whites compared to nonwhites warrants further investigation.

Residents of rural areas (that is, those not living in a metropolitan statistical area) were not underrepresented among intraocular lens recipients. This finding may reflect the general nonemergency nature of intraocular lens implantation so that residents of rural areas may be willing and able to plan for travel to more urban areas to receive intraocular lenses. Low-income recipients were not underrepresented among intraocular lens recipients. As noted previously, Medicare reimbursement may have had a role in this finding.

For over half of the recipients of intraocular lenses, the implant was used for two years or less. This finding is consistent with the rapid increase in the number of cataract extractions in which intraocular lenses were used that occurred between 1983 and 1987, according to data submitted to the Food and Drug Administration from intraocular lens manufacturers. The rate of intraocular lens implantation peaked in the first half of 1987.[4] Also, it is reassuring that the reported replacement rate of the lenses was less than 1%.

Two caveats should be mentioned to aid in the interpretation of the findings of our study. The data indicate that many Americans (an estimated 2.6 million) have intraocular lenses. However, this may be an underestimate of the prevalence because the survey did not include institutionalized people. Nursing-home and boarding-home residents, for example, by age alone, would be expected to have a high prevalence of cataract. Also, the data were acquired by survey response. Medical records were not consulted.

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OPHTHALMIC MINIATURE

If the truth be known, scientists are neither more nor less vain than other people. It is rather that their vanity is the more striking as it appears side by side with their well-known objectivity. The layman is scandalized, but the scandal is not so much the fault of the scientist as it is the layman's canonization of scientists, which the latter never asked for.

Walker Percy, *Love in the Ruins*
New York, Ivy Books, 1971, p. 7

11-0 Mersilene as Running Suture for Penetrating Keratoplasty

Beatrice E. Frueh, M.D., Stuart I. Brown, M.D., and Sandy T. Feldman, M.D.

We evaluated astigmatic results and complications of the combined suturing technique in penetrating keratoplasty by using 11-0 Mersilene as a running suture. Twenty-seven grafts were studied for a follow-up that ranged between ten and 46 months (mean, 27.2 months). During the study, complications included three graft failures, one instance of inadvertent breakage of the running suture, one instance of one suture bite cutting through the recipient cornea, and suture microabscesses in two eyes. Keratometric astigmatism was 2.5 ± 2.1 diopters at six months, was 2.4 ± 2.3 diopters at 12 months, and was 2.5 ± 2.0 diopters at 24 months.

Our data indicate that 11-0 Mersilene is suitable for the running suture in corneal transplants in the combined technique. Spontaneous suture dissolution did not occur throughout the follow-up period. The use of a less biodegradable suture enables the maintenance of low levels of astigmatism for longer periods when compared with a previous study that used 11-0 nylon suture.

POSTOPERATIVE ASTIGMATISM is a common complication after penetrating keratoplasty.[1-3] Several intraoperative factors can contribute to postkeratoplasty astigmatism, such as suturing technique,[4-12] donor-recipient malapposition,[13,14] or trephination technique.[15,16] In the postoperative course, two different approaches are possible. The first technique is to remove all the sutures at a given time postoperatively[10,17,18]; the second is to influence astigmatism by selectively removing interrupted sutures in the presence of a running suture[4-7,11] or by adjusting a single running suture.[9,12,19] The major disadvantage of the first method is that dramatic and unpredictable changes in astigmatism occur frequently after removal of all the sutures, even years postoperatively.[17,28,20] Conversely, not removing the sutures in corneal transplants carries the risk of complications associated with exposed sutures,[21-24] as well as astigmatic changes after spontaneous dissolution.[7]

In a previous study,[7] we described spontaneous breakage of the 11-0 nylon suture in the combined suture technique in nine of 21 eyes (43%) between 13 and 70 months postoperatively, which resulted in a marked increase in astigmatism.[7] Because of this high rate of dissolution, we investigated the use of a less biodegradable and nonhydrolyzable suture, 11-0 Mersilene,[25] as a running suture in the combined suturetechnique for penetrating keratoplasty. We evaluated the long-term astigmatic results and complications in a group of 27 corneal transplants with a running 11-0 Mersilene suture.

Material and Methods

Between February 1987 and November 1989, 102 penetrating keratoplasties were performed by one of us (S.I.B.) at our institution. Seventy-two eyes were omitted from this study because they were considered ineligible for the combined suturing technique because of extensive vascularization (45 eyes), perforation (two eyes), or congenital opacification (25 eyes). Three eyes were excluded because of loss to follow-up between six and seven months postoperatively.

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From the Department of Ophthalmology, University of California at San Diego, La Jolla, California. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York, New York; the Swiss Science Foundation, Bern, Switzerland (Dr. Frueh); and National Institutes of Health Physician Scientist Award AG 000353 (Dr. Feldman).

Reprint requests to Sandy T. Feldman, M.D., University of California at San Diego (0946), Shiley Eye Center, 9500 Gilman Dr., La Jolla, CA 92093-0946.

The surgical technique was similar in all 27 eyes in this study and was previously described.[6] In brief, the donor cornea was cut with a 7.7-mm disposable hand-held trephine and placed in a 7.5-mm recipient bed. Twelve interrupted 10-0 nylon sutures were then placed and a running 11-0 Mersilene suture was sutured with 16 bites. All knots of all sutures were buried. Important aspects of suturing Mersilene included making certain that no visible particulate matter was attached to the suture and that the suture was tied with enough tension to approximate tissue but not so tightly that the suture would cut through the host tissue. Selective removal of interrupted sutures was initiated as early as six weeks postoperatively in the steepest meridian on the basis of central keratometric readings if the astigmatism was more than 2.5 diopters. Additional interrupted sutures were removed only if loosening, breakage, or vascularization occurred. The continuous suture was left in place.

Postoperative data were collected on a standardized form until September 1991 by an independent observer. After an additional surgical procedure, keratometric readings were still recorded, but were not included in the analysis. Data were analyzed with regard to age, gender, preoperative diagnosis, graft clarity, keratometric astigmatism, and best-corrected visual acuity.

The nonparametric, Kaplan-Meier survival analysis method[26] was used to predict the risk of suture disruption with time after penetrating keratoplasty. The survival analysis of Mersilene sutures was compared with that for the 11-0 nylon sutures of our previous study[7] by the Mantel-Haenszel chi-square test.[27]

Results

The preoperative diagnoses of the 27 eyes studied included bullous keratopathy (ten eyes), failed grafts (six eyes), Fuchs' corneal dystrophy (four eyes), keratoconus (three eyes), and other (four eyes). The mean age of the patients at the time of surgery was 63.4 ± 19.1 years (mean ± standard deviation). Twelve patients were men and 15 were women. The mean follow-up was 27.2 months and ranged between ten and 46 months.

The mean keratometric astigmatism was 5.5 ± 3.3 (mean ± standard error of the mean) diopters one month postoperatively (before initiation of selective suture removal). Keratometric astigmatism was further diminished to 2.9 ± 2.3 diopters at three months, 2.5 ± 2.1 diopters at six months, 2.4 ± 2.3 diopters at 12 months, 2.9 ± 1.8 diopters at 18 months, and 2.5 ± 2 diopters at 24 months (Fig. 1). Refractive astigmatism was 2.0 ± 1.2 diopters at six months and 1.9 ± 1.3 diopters at 12 months, respectively. There was no correlation between age at surgery and postoperative astigmatism (r = .0004). There was no difference in astigmatism between the diagnostic groups.

The best-corrected visual acuity was 20/40 or better in 18 of 27 eyes (67%) at six months, in 14 of 26 eyes (54%) at one year, and in 12 of 18 eyes (67%) at two years (Fig. 2). Excluding patients with known extracorneal disease (age-related macular degeneration [two eyes], severe glaucoma [one eye], and dense cataract [two eyes]), 18 of 25 eyes (72%) had 20/40 or better visual acuity at six months, 14 of 22 eyes (64%) had 20/40 or better visual acuity at one year, and 12 of 16 eyes (75%) had 20/40 or better visual acuity at two years.

Kaplan-Meier survival analysis from the time of penetrating keratoplasty to the breakage of the running 11-0 Mersilene suture showed that 100% of the Mersilene sutures remained intact throughout the study.

During this study, three grafts failed despite intensive medical treatment; one of those had reduced transparency caused by recurrent herpes simplex keratitis. One graft developed band keratopathy after cryotherapy because of un-

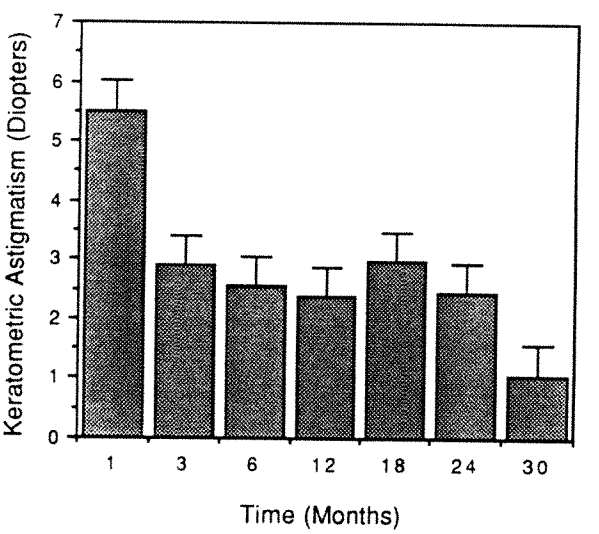


Fig. 1 (Frueh, Brown, and Feldman). Keratometric astigmatism (mean ± standard error of the mean) at varying times after penetrating keratoplasty.

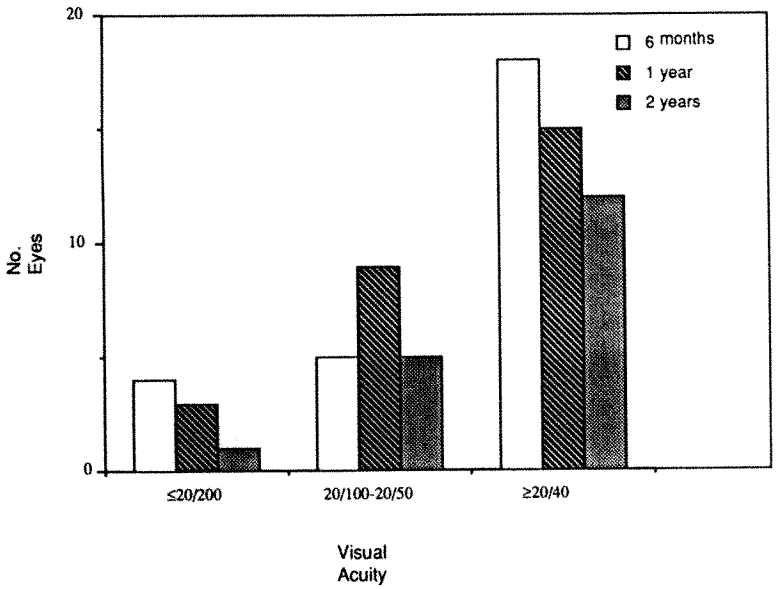


Fig. 2 (Frueh, Brown, and Feldman). Number of eyes having best-corrected visual acuity in one of three ranges: better than or equal to 20/40, 20/50 to 20/100, and worse than 20/200. The number of eyes included in the analysis were 27, 26, and 18 at six, 12, and 24 months, respectively.

controlled glaucoma. In one case, the Mersilene running suture was removed at 24 months because of inadvertent breakage while attempting to remove an adjacent interrupted suture. Thereafter the astigmatism increased by 0.75 diopter, but calculated by vectorial analysis there was a change of 6.75 diopters. No patient developed severe vascularization or loosening of the Mersilene suture. Microabscesses along the Mersilene suture were noted in two eyes during the first postoperative week. These microabscesses were subepithelial and were opened with forceps. They did not recur afterward. In one graft, one bite of the running suture cut through the recipient cornea two years after penetrating keratoplasty, but did not cause complications. None of the eyes required surgical correction of corneal astigmatism. Uncomplicated cataract extraction was performed on three eyes at 12 months (two eyes) and 21 months (one eye) after penetrating keratoplasty. One patient died during this study (after more than 32 months).

Discussion

We analyzed the postkeratoplasty astigmatism and longer-term complications of the combined technique by using 11-0 Mersilene as a running suture. By selectively removing interrupted sutures in the steep axis, the keratometric astigmatism was 2.9 ± 2.3 diopters at three

TABLE 1
MEAN POSTOPERATIVE KERATOMETRIC ASTIGMATISM IN PREVIOUS STUDIES

INVESTIGATORS	SUTURING METHOD	PREADJUSTMENT OR PRESUTURE REMOVAL (DIOPTERS)	POSTOPERATIVE ASTIGMATISM (DIOPTERS)		
			3 MOS	6 MOS	12 MOS
Binder[4]	Combined	7.5	4.1	3.6	3.3
Musch and associates[10]*	Double running	—	3.50	3.00	4.00
	Combined	—	4.00	3.00	2.50
McNeill and Wessels[9]	Control (single running)	5.50	4.80	4.71	—
	Adjusted single running	5.32	2.87	3.23	—
Lin and associates[19]	Single running	6.7	1.9	—	—
	Double running	5.9	5.5	—	—

*In this study, results represent median keratometric astigmatism, not the mean.

months postoperatively, 2.5 ± 2.1 diopters at six months postoperatively, and 2.4 ± 2.3 diopters at 12 months postoperatively. These results are comparable to previously reported data after penetrating keratoplasty in which the combined suturing technique, double running suture, or the single adjustment technique was used (Table 1).[4,9,10,12,19] In one eye, the Mersilene suture had to be removed because of iatrogenic breakage 24 months postoperatively, and in another eye, one bite cut through the recipient cornea, but without consequence. Best-corrected visual acuity in our study was similar to other studies that used the combined technique with running nylon or double running sutures (range, 11 to 13 months postoperatively) (Table 2).[10,11] Significant vascularization was not induced in any eye. Microabscess formation within the first postoperative week along the running Mersilene suture was observed in two eyes. These abscesses were opened with jeweler forceps at postoperative slit-lamp examination and did not recur. These abscesses were sterile. In an animal study, Holland and associates[28] found more corneal inflammation by using Mersilene or Prolene sutures, compared with nylon and stainless steel. To date, we have not found such inflammation. We believe that the low rate of inflammation observed with Mersilene sutures in this study was the result of the careful avoidance of foreign-body adherence to the suture at the time of surgery, as well as the use of this technique in eyes without vascularization.

Our data support the study of Bertram and associates,[29] in which no marked differences in the tissue- or suture-related complications were found when a running 11-0 Mersilene suture was compared to a running 11-0 nylon suture in the combined suturing technique. The same study showed that Mersilene was unsuitable for interrupted sutures or as a single running suture in the adjustment technique. Because of its inelasticity, postoperative manipulation of Mersilene caused notably more cutting through the cornea than nylon. Intraoperatively, Mersilene is less flexible, and misjudgment of the tension resulted in too tight or too loose interrupted sutures.

At four years of follow-up, 100% of the Mersilene sutures remained intact, as compared with our previous study in which only 27.6% of nylon sutures remained intact.[7] Comparison of the Kaplan-Meier curves previously reported for nylon with that for Mersilene in our study, shows statistically significant (P = .015) differences as calculated by the Mantel-Haenszel approach.[27] Because of the lack of spontaneous breakage of 11-0 Mersilene during this study, Mersilene may be superior to nylon for the running 11-0 suture in the combined technique. Nevertheless, because of the previous studies of Holland and associates[28] and Bertram and associates[29] on Mersilene, we advise the use of Mersilene in the combined suture technique only in nonvascularized, noninflamed eyes. With any sutures, but especially with Mersilene, too tight or too superficial intraoperative suture adjustment may cause postoperative cutting of the Mersilene through the recipient or donor cornea and too loose suture adjustment will cause the problems associated with exposed sutures.[21-24]

Our data suggest that the stability of 11-0 Mersilene is superior to 11-0 nylon suture as the running suture in the combined technique; however, longer follow-up is needed to assess if 11-0 Mersilene will degrade later in the postoperative course. The combined suturing technique has a value in the management of astigmatism after penetrating keratoplasty, as long as the running suture does not degrade and break.

TABLE 2
POSTOPERATIVE VISUAL ACUITY IN PREVIOUS STUDIES

INVESTIGATORS	SUTURE TECHNIQUE	NO. OF EYES (%) WITH 20/40 OR BETTER VISUAL ACUITY AT 12 MOS
Musch and associates[10]	Double running	38/54 (70.4)
	Combined	25/54 (46.3)
Stainer, Perl,[11] and Binder	Combined	
	No exclusions	20/34 (59)
	Extracorneal disease	18/27 (67)

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Ocular Involvement in an Outbreak of Herpes Gladiatorum

Edward J. Holland, M.D., Robert L. Mahanti, M.D., Edward A. Belongia, M.D., Martin W. Mizener, M.D., Jesse L. Goodman, M.D., Charles W. Andres, M.D., and Michael T. Osterholm, M.D.

An epidemic of herpes simplex virus type 1 occurred in 60 of 175 wrestlers (34%) attending a four-week intensive training camp. Five of these 60 patients (8%) developed ocular involvement that included follicular conjunctivitis, blepharitis, and phlyctenular disease. Cultures of the conjunctiva and eyelid vesicles were positive for herpes simplex virus type 1 in four of the five patients with ocular disease. The viral isolates were compared by restriction-endonuclease analysis, which disclosed that three of the four isolates were the same strain. None of the patients had corneal involvement and there has been no evidence of viral recurrence to date. Herpes simplex virus type 1 is a health risk for wrestlers, and ocular infections are part of the clinical spectrum. Prompt diagnosis and appropriate management of the outbreak may reduce the severity of the outbreak transmission.

HERPES GLADIATORUM is the term used to describe a cutaneous infection with the herpes simplex virus acquired during participation in contact sports, especially wrestling. The infection is acquired by direct, usually skin-to-skin, contact with an infected individual. Affected individuals develop a characteristic vesicular skin eruption. Constitutional symptoms such as headache, sore throat, and anorexia may develop if the individual has never been exposed to the virus. Limited outbreaks of herpes gladiatorum have been reported.[1-3] Recently, we investigated a large outbreak of herpes gladiatorum. In this outbreak, 60 high-school wrestlers developed herpes gladiatorum, five of whom developed ocular involvement.

Patients and Methods

In July 1989, 175 high-school wrestlers from across the United States participated in a four-week intensive training camp. During the last week of the camp, an outbreak of herpes gladiatorum was identified and investigated by the Minnesota Department of Health, and the Departments of Ophthalmology, Infectious Disease, and Emergency Medicine at the University of Minnesota.

A case of herpes gladiatorum was defined as isolation of herpes simplex virus type 1 from involved skin or mucous membranes, or the presence of cutaneous vesicles as noted by an examining physician. All five patients with ocular involvement were examined by the Cornea Service. Cultures of conjunctiva or eyelid vesicles and serologic studies for herpes simplex virus antibodies were obtained in four of five patients. Three serologic samples were obtained by using an enzyme-linked immunosorbent assay for IgG antibodies to herpes simplex type 1 virus. One serologic sample was obtained 16 days after the onset of symptoms. Restriction-endonuclease analysis was performed on the isolates of herpes simplex virus type 1 obtained from the vesicular lesions on skin or mucous membranes. Oropharyngeal swabs and swabs of skin and mucous membranes were obtained on culturettes and inocu-

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From the Department of Ophthalmology (Drs. Holland, Mahanti, and Mizener), the Division of Infectious Diseases, the Department of Internal Medicine (Dr. Goodman), and the Department of Internal Medicine (Dr. Andres), University of Minnesota Hospital and Clinic, Minneapolis, Minnesota; and the Division of Field Services, Centers for Disease Control Assigned to the Acute Disease Epidemiology Section (Dr. Belongia), and the Acute Disease Epidemiology Section (Dr. Osterholm), Minnesota Department of Health, Minneapolis, Minnesota.

Reprint requests to Edward J. Holland, M.D., Department of Ophthalmology, University of Minnesota, 516 Delaware St. S.E., Minneapolis, MN 55455.

lated within one hour onto rabbit skin cells and human foreskin fibroblasts. High-titer virus stocks were produced from positive cultures by subculturing rabbit skin cells.[4] Viral DNA was isolated from infected rabbit skin cells by ultracentrifugation through sodium iodide gradients.[5] The herpes simplex virus DNA was cleaved with restriction enzymes, *Bam*HI, *Kpn*I, *Eco*RI, *Sal*I, and *Hin*dIII. The endonuclease-cleaved DNA was subjected to electrophoresis in 0.8% agarose gels along with prototype strains, herpes simplex type 1, 17 syn+, and herpes simplex virus type 2 HG52. The gels were stained with ethidium bromide.

Case Reports

Case 1

A 15-year-old boy was examined for conjunctivitis in his right eye. He had been seen in the Emergency Department the previous day when viral conjunctivitis in the right eye and a folliculitis of both arms had been diagnosed. Oral dicloxacillin was prescribed for the folliculitis.

Visual acuity was 20/20 in both eyes. A follicular conjunctivitis in the right eye was evident without preauricular adenopathy. The cornea was normal. External examination disclosed several 1-cm-diameter crusted lesions on the right portion of his forehead and face. These had been formed by facial friction against the wrestling mat, which is more commonly referred to as mat burn. No clustered vesicles were present. No specific treatment was prescribed for the right eye. Two days later the patient returned to the Cornea Service with several vesicles on the right lower eyelid. He also had symptoms of malaise, sore throat, and headache. Primary ocular herpes simplex virus infection was diagnosed, and the patient was then treated with topical vidarabine ointment five times a day. Cultures were not obtained in this case. The lesions of the face and eyelid resolved over a two-week period. He has not had a recurrence of eyelid disease or an episode of ocular injection to date.

Case 2

A 16-year-old boy was examined at the Emergency Department for a vesicular rash on the right portion of his forehead and pustules on his legs (Fig. 1). These vesicles were treated with topical acyclovir ointment. Oral erythromycin was prescribed for the folliculitis on his legs. A viral culture of the skin vesicles on his forehead was positive for herpes simplex virus type 1. He was examined at the Cornea Service four days later because of complaints of an irritated right eye. Visual acuity was 20/20 in both eyes. There was a follicular conjunctivitis in the right eye. The cornea was free of inflammation. A conjunctival culture was positive for herpes simplex virus type 1. Results of serologic studies for herpes simplex virus antibodies were negative. He was treated with a two-week course of topical trifluridine. The follicular conjunctivitis resolved without corneal involvement. He has not had evidence of viral recrudescence.

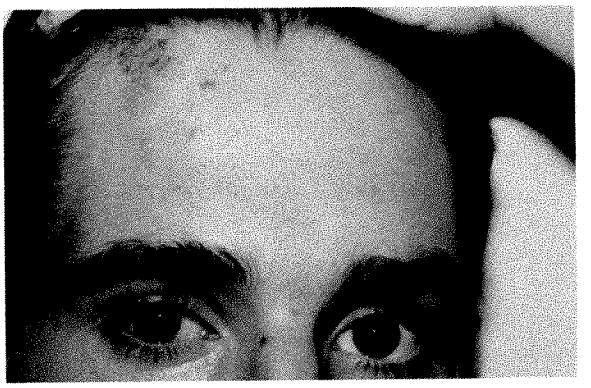


Fig. 1 (Holland and associates). Case 2. Note right forehead vesicular eruption and conjunctivitis of the right eye. Conjunctival cultures grew herpes simplex virus type 1.

Case 3

A 16-year-old boy had a one-day history of redness and irritation in his right eye at initial examination. General examination disclosed vesicles on the right side of his neck, and the fingers of his right hand that had been present for two days. Visual acuity was 20/20 in both eyes. The right lower eyelid had vesicular lesions on the eyelid margin and a follicular conjunctivitis (Fig. 2). The cornea was free of inflammation. Topical vidarabine ointment was prescribed and the patient was removed from participation in wrestling. Viral cultures of the eyelid vesicles were positive for herpes simplex virus type 1. Results of serologic studies for herpes simplex virus antibodies were negative. The follicular conjunctivitis resolved without corneal involvement. He has not had evidence of viral recrudescence.

Case 4

A 16-year-old boy had been seen in the Emergency Department eight days before his ocular complaints for examination of a rash on his

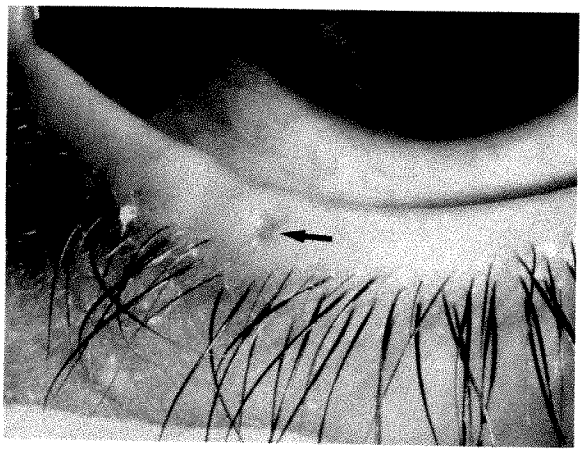


Fig. 2 (Holland and associates). Case 3. Eyelid margin vesicles (arrow). Cultures of these vesicles grew herpes simplex virus type 1.

back. Folliculitis was diagnosed and he was treated with oral dicloxacillin. At this time there were no skin vesicles noted. Eight days later he was admitted to the Cornea Service because of complaints of a red and irritated left eye. Visual acuity was 20/20 in both eyes. Vesicles were seen on the lower eyelid. Additionally, a follicular conjunctivitis was present in the left eye. The cornea was free of inflammation. Culture of the lower eyelid vesicles was positive for herpes simplex virus type 1. Treatment with vidarabine ointment, applied five times a day to the left eye, was initiated. Results of serologic studies for herpes simplex virus antibodies were negative. The blepharoconjunctivitis resolved and he has had no episodes of recurrence.

Case 5

A 16-year-old boy had a two-week history of fever and congestion on admission to the Emergency Department. No rash was present at this time. Sinus films demonstrated an opacified right ethmoid sinus. He was treated with erythromycin and oral decongestants for ethmoid sinusitis. The patient was examined at the Eye Clinic two days later for a 12-hour history of right-eye redness and irritation. Visual acuity was 20/20 in both eyes. An angular blepharitis and follicular conjunctivitis were seen in the right eye. Additionally, there were two limbal phlyctenules (Fig. 3). Gram stain of the lower eyelid was negative for polymorphonuclear leukocytes and bacteria. Conjunctival cultures were positive for herpes simplex virus type 1. Bacterial cultures were negative. The patient was treated with trifluridine drops every two



Fig. 3 (Holland and associates). Case 5. Conjunctivitis with limbal phlyctenules (arrows). Cultures of the conjunctiva grew herpes simplex virus type 1.

hours in the right eye. The patient returned to his home in California and was seen by a local ophthalmologist. He had resolution of the phlyctenules and the follicular conjunctivitis within a week. To date there have been no episodes of viral recrudescence.

Results

Sixty of 175 participants (34%) met the case definition of a herpes simplex viral infection. Five of these 60 patients (8%) had ocular findings. All of these patients had a follicular conjunctivitis. Four of the patients had a blepharitis and one of the patients had limbal phlyctenules. None of the patients had evidence of keratitis. Ocular involvement developed in the third or fourth week of camp in all of the afflicted patients.

The viral cultures of the conjunctiva and eyelids in four of the five patients with ocular findings were positive for herpes simplex virus type 1. Restriction-endonuclease analysis on the isolates demonstrated four distinct herpes simplex type 1 strains. Two strains were from the four isolates from the wrestlers with ocular involvement, with Cases 2, 3, and 4 having the same strain. This strain was also the most common strain identified in the wrestlers without ocular involvement. The patient in Case 5 had a different strain and it was not known whether he trained separately and did not have contact with the other wrestlers with ocular involvement.

Discussion

Herpes gladiatorum was first described in 1964 by Selling and Kibrick.[1] They reported five cases of cutaneous herpes simplex infection over a ten-month period. All affected individuals were members of a group who wrestled regularly at a local gymnasium. In the series of five cases, one patient developed a conjunctivitis and subsequently developed a dendritic keratitis several days later. The patient had a recurrence of the keratitis 16 months later.

In 1984, White and Grant-Kels[2] described herpes gladiatorum in four rugby players.[2] All were exposed to an opposing player who had blisters on his neck. Two patients developed ocular involvement. One patient had a blepharoconjunctivitis without corneal involvement; the other patient had a follicular conjunctivitis and later developed a dendritic keratitis.

We studied a large outbreak of herpes gladiatorum in which 60 of 175 wrestlers who participated in intensive training camp were affected. The complete epidemiologic as well as laboratory investigations of this outbreak have been recently reported.[6] Restriction-endonuclease analysis identified four distinct strains of herpes simplex virus type 1 among the 21 viral isolates. The cultures of the conjunctiva and eyelid vesicles were all positive for herpes simplex virus type 1 in four of the five patients with ocular involvement. Two different strains were identified among the four ocular isolates. Three of the four wrestlers had the same strain and this strain was the most common strain identified in the wrestlers without ocular involvement.

In adults, herpes simplex viral infections are transmitted primarily through close personal contact. Sources of virus include recrudescent herpetic lesions, and asymptomatic pharyngeal shedding of virus. Autoinoculation from one body site to another can also occur. It is possible that four of the five ocular infections in this outbreak were the result of autoinoculation from preexisting vesicular lesions or mat burns. For example, the patient in Case 4 was a contact-lens wearer who developed ocular involvement eight days after acquiring herpes gladiatorum. Ocular infection with the herpes simplex virus can cause a blepharitis, follicular conjunctivitis, keratitis, scleritis, and uveitis. In our series, all patients with ocular involvement had a follicular conjunctivitis, four had a blepharitis, and one had phlyctenular disease. To date there have been no episodes of viral recrudescence in any of these patients.

Of interest is the patient in Case 5, who developed limbal phylctenules, blepharitis, and a follicular conjunctivitis. Phlyctenular disease is a hypersensitivity response most often associated with staphylococcal infections. Phlyctenules can be associated with viral infections as well,[7] although this is rare. We believe that all of the ocular findings in Case 5 were related to herpes simplex virus infection. This is clinically important as topical corticosteroids are commonly used in the management of phlyctenular disease. Use of topical corticosteroids in Case 5 could have facilitated spread of herpes simplex virus infection to the cornea.

Herpes simplex virus has an incubation period of two to 20 days before manifestations of infection appear.[8] The one-month duration of camp allowed sufficient exposure and incubation time for an epidemic to occur and to be recognized. The intensity of training and the frequency of direct skin-to-skin contact increased the risk of contact and colonization of the virus. Many cases became manifest during the last two weeks of the camp. Had the camp been of shorter duration, the epidemic would have been hard to document, as the participants would have returned to their homes across the United States.

In this outbreak, the percentage of wrestlers with antibodies to herpes simplex virus (indicating previous exposure to the virus) was low. Approximately 25% of white 14-year-olds and 70% of black 14-year-olds have antibodies to herpes simplex virus type 1.[7] The participants in this camp were predominantly white (89%). Because the percentage of wrestlers who were seropositive to herpes simplex virus was low, there was an increased risk of infection. Individuals with antibody to herpes simplex virus are less likely to acquire the infection and if they do, may be less likely to be symptomatic. We believe that all of these cases were a form of primary ocular herpes simplex. Results of serologic studies performed near the time of initial examination in four of these patients were negative for herpes simplex virus antibody.

Measures to prevent spread of herpes gladiatorum should include routine skin examinations before wrestling contact and exclusion of wrestlers with suspicious lesions. Studies of herpetic vesicular lesions have shown recovery of virus up to four days after crusting of vesicles.[9] It is recommended that athletes refrain

from contact for five days after the lesions have dried and crusted.

The risk of these patients to develop a keratitis with subsequent corneal scarring and vision loss is a concern. The risk of developing a keratitis after herpetic blepharoconjunctivitis appears to be low. Liesegang[10] reported that of 45 patients who had only eyelid or conjunctival involvement as their first manifestation of ocular herpes simplex infection, only one developed a recurrence that resulted in deep corneal scarring. However, in published reports on herpes gladiatorum, two of the three patients with ocular infections developed a dendritic keratitis.[1-3]

Those individuals involved in the sport of wrestling (athletes, trainers, coaches, and parents) should be educated as to the cause of herpes gladiatorum and the measures to prevent transmission. Ophthalmologists should be aware of this condition, as prompt diagnosis and appropriate exclusion of affected wrestlers may reduce the risk of ocular infections and vision loss.

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OPHTHALMIC MINIATURE

"Can't make it?" the doctor asked. "This is surgery, not a hair appointment. We're talking about your eyesight!"

"I'm busy that day," the young woman said.

"Miss Wilson, maybe you don't understand. This is the kind of problem you take care of *now*, you take care of *yesterday*. Not next week or next month. I can't state that too strongly."

"Yes, but I happen to be occupied that day," the young woman said.

Anne Tyler, *Saint Maybe*
New York, Alfred A. Knopf, 1991, p. 167

The Use of Polymerase Chain Reaction for the Detection of Chlamydial Keratoconjunctivitis

Audrey R. Talley, M.D., Francisco Garcia-Ferrer, M.D., Keith A. Laycock, Ph.D., Michael Loeffelholz, Ph.D., and Jay S. Pepose, M.D.

Ocular swabs from 30 consecutive patients with follicular conjunctivitis were screened for *Chlamydia trachomatis*, herpes simplex virus, and adenovirus by a variety of laboratory techniques. For the detection of *C. trachomatis*, we compared two polymerase chain reaction methods, McCoy cell culture isolation, and the direct fluorescein-conjugated monoclonal antibody test. Four of 30 patients tested positive for *C. trachomatis* by using both conventional and biotinylated polymerase chain reaction methods. Two of the four patients were also McCoy cell culture-positive for *C. trachomatis* and one of four patients tested positive by using a fluorescein-conjugated chlamydial monoclonal antibody test. All four patients responded to oral antibiotic treatment. On follow-up testing, all four patients were polymerase chain reaction-negative, McCoy cell culture-negative, and fluorescein-conjugated antibody test-negative for *C. trachomatis*. The polymerase chain reaction appears to be an equally specific and more sensitive method than McCoy cell culture or fluorescein-conjugated antibody testing for the detection of *C. trachomatis* from ocular specimens.

Chlamydia trachomatis is the most common cause of sexually transmitted disease and of ophthalmia neonatorum in many parts of the world today, including the United States.[1] Additionally, *C. trachomatis* is an increasingly frequent cause of adult keratoconjunctivitis. The prevalence of chlamydial infections of the genital tract in Western populations has been estimated to be 10% to 25%, with 3 to 4 million *C. trachomatis*–related cases of sexually transmitted disease developing annually[2] in the United States. The increasing prevalence of chlamydial disease has generated much interest in the development of sensitive, specific, and rapid laboratory methods for the diagnosis of chlamydial infections.

Ocular signs of untreated chlamydial infection include corneal epithelial keratitis, subepithelial and anterior stromal inflammation, limbal keratitis and pannus formation, focal corneal neovascularization and scarring, and chronic inclusion conjunctivitis.[3,4] In cases of chlamydial ophthalmia neonatorum, up to one third of affected infants may develop chlamydial pneumonitis.[5]

The causative agent, *C. trachomatis*, is an obligate intracellular organism that requires susceptible cells in tissue culture for in vitro propagation. McCoy cell culture is considered the standard for chlamydial diagnosis, with a specificity of 100%, but a sensitivity that varies from 65% to 85%. Additionally, efficient isolation in cell culture requires that the sample be plated as quickly as possible and stored under optimal conditions to maintain the infectious elementary bodies. The results of chlamydial isolation in McCoy cell culture are often not available for 72 hours, depending on the initial inoculum. This may be especially difficult in cases of neonatal chlamydial conjunctivitis, in which the load of elementary bodies may be low at the time of birth. Other techniques of chlamydial detection include use of a direct fluorescein-conjugated antibody (Chlamydiatrak, Syva Corporation, Palo Alto, California), enzyme-linked immunosorbent assay (ELISA) (Chlamydiazyme, Abbott Laboratories, North

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From the Departments of Ophthalmology and Visual Sciences (Drs. Talley, Garcia-Ferrer, Laycock, and Pepose) and Pathology (Dr. Pepose), Washington University School of Medicine, St. Louis, Missouri; and Roche Molecular Systems (Dr. Loeffelholz), Branchburg, New Jersey. This study was supported in part by grants from Roche Molecular Systems, Branchburg, New Jersey (Dr. Pepose); and Research to Prevent Blindness, Inc., New York, New York.

Reprint requests to Jay S. Pepose, M.D., Department of Ophthalmology and Visual Sciences, Box 8096, Washington University School of Medicine, 660 S. Euclid Ave., St. Louis, MO 63110.

Chicago, Illinois), and deoxyribonucleic acid (DNA) probe assay (PACE, GenProbe, San Diego, California). These methods have suboptimal specificities and sensitivities,[6-9] estimated at 81% to 99% specificity and 80% to 99% sensitivity for the direct fluorescein-conjugated antibody; 97% to 98% specificity and 85% to 97% sensitivity for the ELISA; and 95% to 99% specificity and 60% to 93% sensitivity for the direct chemiluminescent-labeled DNA probe assay, respectively, in the detection of *C. trachomatis* in cervical swabs.

Recently, the polymerase chain reaction has been used for the detection of *C. trachomatis* from urogenital specimens. Results of these studies[10,11] indicated an equal specificity and increased sensitivity of the polymerase chain reaction test compared with McCoy cell culture isolation. We adapted the polymerase chain reaction technique for use with ocular specimens. We compared chlamydial detection from ocular swabs by using McCoy cell culture, direct fluorescein-conjugated antibody staining, and standard and biotinylated polymerase chain reaction techniques.

Material and Methods

Patient selection—From October 1990 through August 1991, we examined 30 consecutive patients (age range, 4 weeks to 47 years) at the cornea service at Washington University Medical Center who had a diagnosis of follicular conjunctivitis. All patients were subjected to the following studies in an effort to determine the origin of the follicular conjunctivitis.

Specimen collection—Conjunctival swab specimens were obtained from each patient by vigorously swabbing the conjunctival fornix with a Dacron cytoswab (Xomed-Treace, Jacksonville, Florida). Swabs were first rolled onto a Chlamydiatrak slide (Syva Corporation) for direct fluorescein-conjugated antibody staining for chlamydial elementary bodies and then placed in a 1.5-ml vial of Centers for Disease Control chlamydial transport medium and divided into aliquots for polymerase chain reaction and McCoy culture techniques. Aliquots for polymerase chain reaction and culture were then frozen at −20 C or refrigerated at 4 C, respectively, and were processed within 24 hours of collection. Additional conjunctival swab specimens were obtained in the same manner for adenovirus and herpes simplex virus respectively, and were placed in viral transport media at 4 C.

Isolation of adenovirus in tissue culture—Samples were vortexed for 30 seconds and then centrifuged for ten minutes at 360 rpm. The cell pellet was mixed with phosphate-buffered saline solution and placed in a well on a slide. Slides were allowed to air dry and were then fixed with acetone for ten minutes at −20 C. Slides were then stained with Bartels (Baxter Corporation, West Sacramento, California) anti-adenovirus monoclonal antibody for 30 minutes and incubated for an additional 30 minutes with fluorescein isothiacyanate–conjugated antimouse IgG antibody according to the manufacturer's directions. Slides were read by using a fluorescent microscope and graded as positive if there was marked apple-green fluorescence.

Supernatant from the vortexed sample vials was mixed with 0.3 ml of a mixture of penicillin, streptomycin, and amphotericin and incubated for 30 to 60 minutes at room temperature (23 C). A 0.3-ml sample was placed into one MRC-5 fibroblast tissue culture tube, one rabbit kidney tissue culture tube, and one human embryonic kidney tissue culture tube, and incubated at 36 C for one hour. Fresh media were then placed into the sample tubes, incubated overnight, and read daily for seven days and graded for viral cytopathic effect.

Isolation of herpes simplex virus in tissue culture—Samples in viral transport medium were mixed with 0.3 ml of tissue culture medium that contained penicillin, streptomycin, and amphotericin and incubated at 23 C for 30 to 60 minutes. A 0.3-ml aliquot of this sample mixture was then transferred into one MRC-5 fibroblast tissue culture tube and into one rabbit kidney tissue culture tube and incubated at 36 C for one hour. Fresh complete tissue culture media were then placed into the sample tubes, which were read daily for seven days and graded for viral cytopathic effect. All positive samples were confirmed by fluorescein antibody staining method by using anti-herpes simplex virus antibody (Syva Corporation) as previously described, according to the manufacturer's directions.

Isolation of C. trachomatis in McCoy cell culture—Samples for isolation of *C. trachomatis* in McCoy cell culture were vortexed and the media were divided into two shell vials. Vials were

centrifuged for 60 minutes at 360 rpm and the media were inoculated into cycloheximide-treated McCoy cell monolayers, and incubated at 37 C for 40 hours. After this first pass, cells were stained and read in the usual manner, and compared to a reference strain of *C. trachomatis*. A second pass was then performed in the same manner and a final reading was done 40 hours after the first pass.

Direct fluorescein-conjugated antibody staining for C. trachomatis—Swabs of the ocular surface were rolled over the surface of the Chlamydiatrak slide (Syva Corporation), allowed to air dry, and were fixed with acetone that was provided in the Chlamydiatrak kit. Slides were then fixed again with methanol and stained with the Microtrak (Syva Corporation) fluorescein-conjugated monoclonal antibodies according to the manufacturer's directions. Smears were allowed to dry at room temperature for 15 minutes and slides were evaluated under a fluorescence microscope. Slides were scored as positive if at least ten elementary bodies were visualized.

Polymerase chain reaction amplification of chlamydial nucleic acid—Samples were thawed to 23 C and then boiled for 15 minutes in a water bath to release DNA. Aliquots (20 μl) were placed in a polymerase chain reaction mixture that contained the following: (1) 5 μl of 10 × polymerase chain reaction buffer (Promega, Madison, Wisconsin), (2) 8 μl of 1.25-mmol/l deoxyadenosine triphosphate/deoxycytosine triphosphate/deoxyguanine triphosphate/thymidine triphosphate, (3) 2.5 μl of a 20-mmol/l solution of oligonucleotide primers specific for the major outer-membrane protein gene: CT1: CCT/GTG/GGG/AAT/CCT/GCT/GCT/GAA and CT4: GTC/GAA/AAC/AAA/GTCATCCAGTA/GTA, and (4) 1 μl (2.5 units) of thermostable Taq DNA polymerase (Promega, Madison, Wisconsin). The reaction mixture was then brought up to a volume of 50 μl by the addition of deionized sterile water and was overlaid with 50 μl of paraffin oil. Samples were placed in a thermal cycler (Coy Corporation, Grass Lake, Michigan) and denatured for five minutes at 94 C, and subjected to 40 cycles of amplification by using the following procedures: (1) denaturation at 94 C for two minutes, (2) annealing at 52 C for one minute, and (3) primer extension at 72 C for two minutes. After the last cycle, samples were incubated for seven minutes at 72 C.

We then analyzed 20 μl of each reaction mixture sample by gel electrophoresis (12% acrylamide or 2% agarose). The 144 base pair reaction products were visualized by staining with ethidium bromide and photographed under ultraviolet illumination. Positive and negative chlamydial DNA samples and a reagent blank containing all the components of the reaction mixture but no DNA were included in every polymerase chain reaction procedure. Bands visualized were compared with DNA molecular weight markers.

Southern blot analysis confirmation of polymerase chain reaction—Southern blot hybridization was performed on DNA bound to nylon membrane (Hybond, Amersham, Arlington Heights, Illinois) by overnight capillary transfer and fixed by ultraviolet radiation for five minutes. Prehybridization was performed overnight at 37 C in 0.9-mol/l NaCl, 90-mmol/l sodium citrate, pH 7.0 (6 × standard saline citrate), 5 × Denhardt's solution, 5% sodium dodecyl sulfate, and 100-μg/ml denatured salmon sperm DNA, followed by hybridization with ^{32}P-labeled internal probe[12] 5'CCATCA/GAATTCCGTCGATCAT3' at 37 C in the same solution as mentioned previously with the addition of 100-μg/ml diethylaminoethyldextran sulfate. Membranes were washed twice for 20 minutes each with 6 × standard saline citrate at 23 C and were autoradiographed.

Biotinylated polymerase chain reaction—Specimens were collected in culture transport medium. An aliquot of culture transport medium was combined with an equal volume of STD Specimen Diluent (Roche Molecular Systems, Branchburg, New Jersey) that contained $MgCl_2$ and was heated at 90 C for 15 minutes. A 50-μl aliquot of the treated specimen was added to 50 μl of 2 × polymerase chain reaction buffer (Amplicor, Chlamydia Master Mix, Roche Molecular Systems). Chlamydia Master Mix contained biotinylated oligonucleotide primers directed against the *C. trachomatis*–specific cryptic plasmid, dNTPs (with dUTP replacement of dTTP), Tris buffer, KCl, glycerol, uracil-N-glycosylase (Amp Erase, Roche Molecular Systems) (to prevent carry-over contamination), and Taq DNA polymerase.

Alternatively, some specimens were extracted once with phenol/chloroform/isoamyl alcohol (25:24:1), followed by a single extraction with chloroform/isoamyl alcohol (24:1). Extracted nucleic acids were precipitated with ethanol and suspended in the original volume of STD Sample Transport Medium/STD Speci-

men Diluent (1:1). A 50-μl aliquot of the extracted, suspended nucleic acid was added to 50 μl of 2 × Chlamydia Master Mix.

Using a Perkin Elmer TC9600 thermal cycler (Perkin Elmer, Norwalk, Connecticut), specimens in Amplicor Chlamydia Master Mix were subjected to an initial five-minute cycle at 95 C and a one-minute cycle at 60 C, followed by 29 cycles of 30 seconds at 95 C and one minute at 60 C. After temperature cycling, samples were held at 72 C. Each amplification run contained several negative and positive control samples (uninoculated STD Sample Transport Medium and *C. trachomatis* cryptic plasmid DNA, respectively).

Detection of polymerase chain reaction products—Biotinylated, amplified DNA was denatured by the addition of 100 μl of Denaturation Solution (Roche Molecular Systems) and was hybridized for one hour at 37 C to a specific oligonucleotide probe bound to microtiter plate wells (Silver, S., Sulzinski, M., Buonagurio, A., Barone, A., Liu, P., Lin, P., Emmerling, E., and Keys, L., unpublished data, 1992). After washing away unhybridized material, avidin horseradish peroxidase conjugate (Roche Molecular Systems) was added to plate wells and incubated for 15 minutes at 37 C. Wells were then washed again, followed by the addition of horseradish peroxidase substrate (peroxide/tetramethylbenzidine, Roche Molecular Systems). Color was allowed to develop for ten minutes, after which Stop Solution (Roche Molecular Systems) was added. The absorbance of wells was read at 450 nm in an ELISA reader. Wells generating an absorbance greater than or equal to 0.250 were considered to represent specimens positive for *C. trachomatis*.

Precautions against contamination and false-positive results in polymerase chain reaction—Gloves were always worn during processing of specimens. All reagents were aliquoted using positive-pressure pipettes before the addition of clinical or control samples. Negative and blank reagents were added before positive control or unknown clinical samples. Deoxyribonucleic acid amplification assays of the same specimens were repeated at least three times and on different days and always produced the same results.

Posttreatment laboratory studies—All samples positive for *C. trachomatis* by polymerase chain reaction culture or direct fluorescein-conjugated antibody were reported to physicians. Patients with positive results of polymerase chain reaction, culture, or direct fluorescein-conjugated antibody staining were treated with oral erythromycin or tetracycline for at least two weeks. Posttreatment samples for polymerase chain reaction, culture, and direct fluorescein-conjugated antibody staining were obtained and processed in the same manner as previously described.

Results

Of 30 consecutive cases of follicular conjunctivitis (Fig. 1), three were culture-positive for herpes simplex virus, six (20%) were culture-positive for adenovirus, and four (13%) had laboratory evidence of chlamydial keratoconjunctivitis. No etiologic laboratory diagnosis was made in 17 cases (57%) (Table 1). Ocular swabs from four of 30 patients (13%) with follicular conjunctivitis in this study were positive for chlamydial DNA by the polymerase chain reaction method (Table 2). Bands of 144 base pairs were seen on acrylamide gels (Fig. 1). The authenticity of the reaction product as chlamydial DNA was confirmed by Southern blot hybridization (Fig. 2). Of these four samples, two were also positive by McCoy cell culture. Another polymerase chain reaction–positive sample was direct fluorescein-conjugated antibody–positive, but McCoy cell culture–negative. The fourth sample was direct fluorescein-conjugated antibody– and McCoy cell culture–negative.

Of the four patients with ocular samples positive by the chlamydial polymerase chain reaction, three were sexually active males aged 15, 23, and 41 years, and one was a 4-week-old girl whose mother was at high risk for chlamydial infection. Samples from the 4-week-old girl and 23-year-old man were plated within eight hours of collection and were both culture- and polymerase chain reaction–positive, but direct fluorescein-conjugated antibody–negative. The

TABLE 1
ETIOLOGIC LABORATORY DIAGNOSIS OF FOLLICULAR CONJUNCTIVITIS IN 30 SPECIMENS

	NO. OF SPECIMENS (%)
C. trachomatis	4 (13)
Herpes simplex virus	3 (10)
Adenovirus	6 (20)
No cause	17 (57)

TABLE 2
COMPARISON OF LABORATORY METHODS FOR THE DETECTION OF *C. TRACHOMATIS* FROM SWABS OF THE OCULAR SURFACE

	LABORATORY TECHNIQUE			
NO. OF SPECIMENS TESTED	POLYMERASE CHAIN REACTION	BIOTINYLATED POLYMERASE CHAIN REACTION	McCOY CELL CULTURE	DIRECT FLUORESCEIN-CONJUGATED ANTIBODY
2	Positive	Positive	Positive	Negative
1	Positive	Positive	Negative	Positive
1	Positive	Positive	Negative	Negative

sample for the 15-year-old boy was plated onto McCoy cells within three hours of collection and was polymerase chain reaction–positive, but direct fluorescein-conjugated antibody– and culture-negative. The samples for the 41-year-old man were plated onto McCoy cells within 24 hours and were polymerase chain reaction– and direct fluorescein-conjugated antibody–positive, but McCoy cell culture–negative.

All four polymerase chain reaction–positive samples were also positive by using a biotinylated polymerase chain reaction with plasmid primers in an independent laboratory, which confirmed the results of our standard polymerase chain reaction with major outer-membrane protein gene primers. Follow-up samples were obtained from all four polymerase chain reaction–positive patients who had been treated for two to three weeks with oral erythromycin or tetracycline. These follow-up samples were negative for *C. trachomatis*, by culture, direct fluorescein-conjugated antibody staining, and both standard and biotinylated polymerase chain reaction.

Discussion

In this comparison of three laboratory methods for the diagnosis of chlamydial keratoconjunctivitis, all McCoy cell culture–positive and direct fluorescein-conjugated antibody–positive specimens were also polymerase chain reaction–positive for *C. trachomatis*. The sample that was direct fluorescein-conjugated antibody– and polymerase chain reaction–positive but culture-negative was not plated until approximately 24 hours after sample collection, which may have accounted for the false-negative culture result. The sample that was polymerase chain reaction–positive but direct fluorescein-conjugated antibody– and culture-negative was plated within three hours of sample collection. A low level of infectious elementary bodies or clinical sample toxicity to McCoy cell culture monolayers may have accounted for this false-negative culture result.

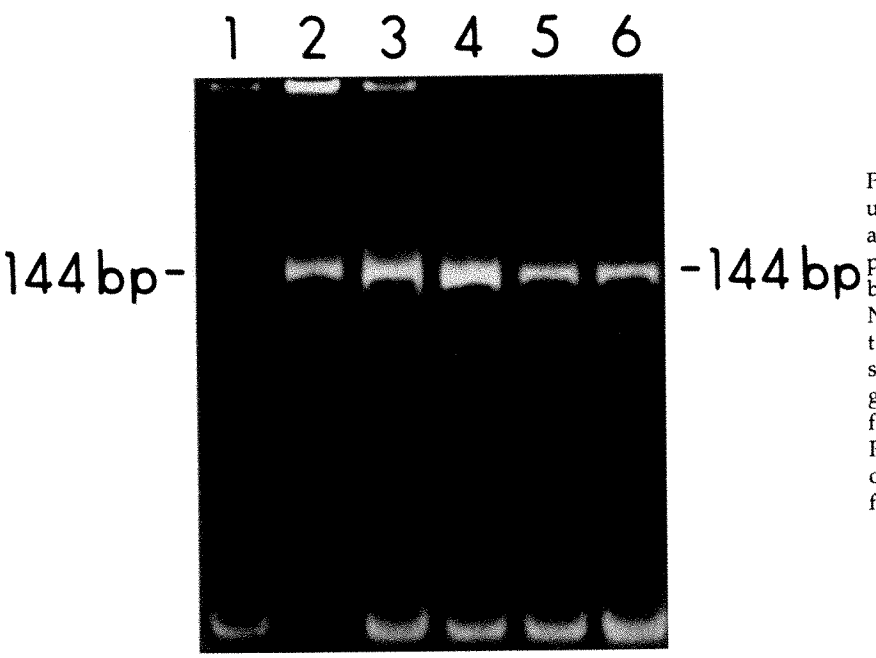


Fig. 1 (Talley and associates). Polymerase chain reaction products of *C. trachomatis* were visualized on an acrylamide gel. The predicted positive band of 144 base pairs is indicated. Lane 1, Negative control. Lane 2, Positive control. Lane 3, Positive sample from a 4-week-old baby girl. Lane 4, Positive sample from a 15-year-old boy. Lane 5, Positive sample from a 23-year-old man. Lane 6, Positive sample from a 41-year-old man.

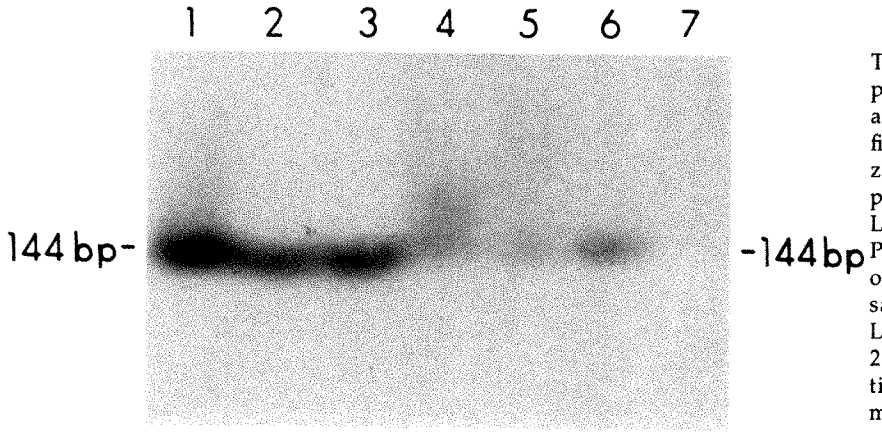


Fig. 2 (Talley and associates). The authenticity of the 144 base pair polymerase chain reaction amplification product was confirmed by Southern blot hybridization with a complementary probe. Lane 1, Positive control. Lane 2, Positive control. Lane 3, Positive sample from a 4-week-old baby girl. Lane 4, Positive sample from a 15-year-old boy. Lane 5, Positive sample from a 23-year-old man. Lane 6, Positive sample from a 41-year-old man. Lane 7, Negative control.

The polymerase chain reaction results in amplification of portions of chlamydial DNA dictated by the selection of primer sequences. In the course of 40 thermal cycles, this segment of DNA is amplified 1 millionfold, which results in a strong signal on acrylamide gel electrophoresis. Our choice of primers complementary to sequences of the major outer-membrane protein gene was based on previously published studies.[12,13] Holland, Gaydos, and Quinn[12] found that all *C. trachomatis* serovars were easily detected with the same intensity by using primers directed against the major outer-membrane protein gene. Dutilh and associates[14] found no cross reactivity with DNA from 11 other bacterial species by using polymerase chain reaction with major outer-membrane protein gene primers. Other primer sequences published for use with chlamydial polymerase chain reaction have included those complementary to the gene encoding the 16S ribosomal RNA[14,15] and to endogenous plasmid.[10] We received independent confirmation of polymerase chain reaction–positive specimens from our laboratory by an independent laboratory that used primers complementary to endogenous plasmid sequences.

The possibility of false-positive polymerase chain reaction results in this study is unlikely. All polymerase chain reaction–positive specimens were positive with two sets of primers in two independent laboratories on at least three occasions at different times or with different staff members, or both. All polymerase chain reaction samples from the major outer-membrane protein primer amplifications were also confirmed by using Southern blot hybridization. The incorporation of dUTP/uracil-N-glycosylase into the biotinylated polymerase chain reaction system has been demonstrated to eliminate up to 10^5 copies of contaminating polymerase chain reaction product. Additionally, follow-up results of polymerase chain reaction, culture, and direct fluorescein-conjugated antibody tests all became negative on retesting of all patients after oral antibiotic treatment.

Although inferences from our study may be limited by the small sample size, these data suggest an equal specificity and increased sensitivity of the polymerase chain reaction method when compared to the reference method of McCoy cell culture. This correlates well with previous studies on urogenital specimens. Use of the polymerase chain reaction with plasmid primers[10] to test 215 genital specimens and eight conjunctival specimens from newborns disclosed that 26 (24 genital and two conjunctival) were both McCoy cell culture–positive and polymerase chain reaction–positive for *C. trachomatis*. An additional 14 specimens (13 genital and one conjunctival) were polymerase chain reaction–positive but were culture-negative for *C. trachomatis*. Pao and associates[16] published a study of intra-amniotic detection of *C. trachomatis* by using polymerase chain reaction with major outer-membrane protein gene primers. In that series, five of 31 endocervical specimens and one of nine amniotic fluid specimens were positive for *C. trachomatis* by both culture and polymerase chain reaction. An additional four endocervical and one amniotic fluid specimens were polymerase chain reaction–positive but were culture-negative. Dean, Pant, and O'Hanley[17] compared serial tissue culture passage with polymerase chain reaction–amplified DNA probe for conjunctival specimens from patients from Nepal with trachoma. In that study of 252 specimens from patients with

clinical trachoma, only 32% of the *C. trachomatis*–positive specimens were detected by cell culture, compared with 90% detected by polymerase chain reaction. All of these studies support our preliminary findings, that the polymerase chain reaction may have greater sensitivity and may depend less on immediate plating and transport, as compared to isolation in McCoy cell culture.

The distribution of causes of follicular conjunctivitis in our study is similar to that of previous studies. Potts and associates[18] found that 19 of 178 patients (11%) with follicular conjunctivitis who were examined at an ophthalmic casualty department yielded positive results on chlamydial testing with direct immunofluorescent antibody testing. The etiologic diagnosis of the remaining patients in their study was not disclosed. Fitch and associates[19] studied 45 patients with acute conjunctivitis who were examined at an inner-city emergency room. A viral origin was found in 16 cases (36%), of which 14 patients were infected with adenovirus and one with herpes simplex virus. Bacterial origins accounted for 18 cases (40%). In 11 patients (24%), no etiologic laboratory diagnosis was achieved and no chlamydial conjunctivitis was diagnosed. However, four of the 45 samples were not processed for chlamydial culture. The small sample size, delays in plating the samples onto McCoy cells, and the loss of four samples may have accounted for the lack of chlamydial diagnosis in the study by Fitch and associates.[19] Our finding of four of 30 patients (13%) with laboratory evidence of chlamydial conjunctivitis agrees with the findings of Potts and associates[18] and the demonstration of a viral origin in nine of 30 cases (30%) of follicular conjunctivitis corroborates the results of Fitch and associates.[19]

The polymerase chain reaction is a laboratory research technique that provides a sensitive, specific, rapid method of detection of *C. trachomatis* that can lead to earlier diagnosis and treatment of chlamydial infection and prevention of long-term sequelae. When compared to the standard polymerase chain reaction with Southern blot confirmation, the biotinylated polymerase chain reaction gave identical results with the samples tested. This newly developed technique confirms the amplification product by using solid-phase hybridization followed by colorimetric development in a standard ELISA format. Confirmed results of the biotinylated polymerase chain reaction assay were available in four hours, as opposed to 12 to 24 hours with the conventional polymerase chain reaction/Southern blot hybridization method. Compared to the standard polymerase chain reaction with Southern blot analysis confirmation, the rapid and semiautomated biotinylated polymerase chain reaction technique may prove more practical and amenable to standardization in the diagnostic laboratory setting.

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OPHTHALMIC MINIATURE

The stag at eve, dipping to drink his fill, has his lower *antler* before his eyes. To the Romans, this was the *ramum ante ocularis,* the branch before the eyes: the *ante ocular*—fused in OFr. to *antoillier,* whence early Eng. *antolier, auntelere,* and finally *antler.* When the word came to be applied the any of the branches of the horn, the low one was called the *brow-antler.*

Joseph T. Shipley, *Dictionary of Word Origins*
New York, Philosophical Library, 1945, p. 25

Surgical Management of Myokymia of the Superior Oblique Muscle

Luis C. de Sa, M.D., William V. Good, M.D., and Creig S. Hoyt, M.D.

In the past 15 years, we have examined 20 patients in whom myokymia of the superior oblique muscle was diagnosed. Medical treatment (carbamazepine) failed in three patients, and one patient did not accept drug therapy. These four patients (20%) were operated on for persistent oscillopsia and diplopia. One patient underwent only a superior oblique muscle myotomy, but required an inferior oblique muscle myectomy six months later because of iatrogenic superior oblique muscle palsy. The other three patients underwent simultaneous superior oblique muscle myotomy and inferior oblique muscle myectomy. The symptoms resolved postoperatively in all four patients. Symptomatic patients with superior oblique muscle myokymia in whom medical treatment fails or is intolerable can benefit from surgical treatment consisting of combined superior oblique muscle/inferior oblique muscle myectomy.

SUPERIOR OBLIQUE MUSCLE myokymia is an unusual eye movement disorder characterized by unilateral vertical and torsional microtremor. It was first noted by Duane[1] in 1906, but Hoyt and Keane[2] defined and named this particular entity in 1970.

The disorder is usually chronic and not caused by marked central nervous system disease, although it has been associated with intracranial tumor[3] and adrenoleukodystrophy.[4] Symptoms can last months or years and pose an important and troubling visual handicap.

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From the Department of Ophthalmology, University of California, San Francisco, California. This study was supported in part by a Fellowship in Pediatric Ophthalmology from the Conselo Nacional de Desenvolvimento Cientifico e Tecnologico, San Palo, Brazil (Dr. de Sa).

Reprint requests to William V. Good, M.D., 400 Parnassus No. 704A, San Francisco, CA 94143.

Clinical treatment has been variably successful with carbamazepine,[5-7] beta blockers,[8] baclofen,[6,9] phenytoin,[6,10] and benzodiazepines.[6,9] We treated four patients in whom long-term medical treatment had failed or was intolerable. These patients were operated on when symptoms failed to remit.

Patients and Methods

We reviewed the records of the four patients with superior oblique muscle myokymia who underwent surgical treatment at our institution from January 1977 to March 1992. Preoperatively, all these patients had been medically treated with at least a trial of carbamazepine (with the exception of one patient who did not accept drug therapy). During the same period, 16 other patients in whom superior oblique muscle myokymia was diagnosed were seen at our institution, and none required surgical treatment. The symptoms resolved in all 16 patients either with time alone, or with medication (carbamazepine, specifically). Surgical treatment was offered to patients in whom medical treatment failed, or who could not tolerate the side effects.

There were three women and one man. The left eye was affected in three patients and the right eye was affected in one. The mean age at onset (onset determined on the basis of symptoms) was 31 years (range, 25 to 36 years). Follow-up ranged from two months to 11 years.

Superior oblique muscle tenotomy was performed on the temporal side of the superior rectus muscle, and inferior oblique muscle myectomy was performed simultaneously. The superior oblique muscle tenotomy was performed after careful dissection of the conjunctiva and Tenon's fascia, and identification of the superior rectus muscle. The superior oblique muscle tendon was grasped with a tenotomy hook temporal to the superior rectus muscle. All

fibers were included, and the tendon was cut with sharp dissection. The inferior oblique muscle myectomy was performed by opening the conjunctiva and Tenon's fascia 10 mm from the corneoscleral limbus in the inferotemporal quadrant. The muscle was grasped with tenotomy hooks, cleaned of its fascial attachments, and then grasped with clamps, approximately 3 mm apart. Then a segment of muscle was removed. These techniques are described in further detail elsewhere.[11] One of us (C.S.H.) performed the operation on all four patients.

Results

Patient 1 underwent only superior oblique muscle tenotomy. Postoperatively, she had persistent diplopia caused by a secondary superior oblique muscle palsy. An inferior oblique muscle myectomy, performed six months later, cured the diplopia. The other three patients underwent simultaneous superior oblique muscle tenotomy and inferior oblique muscle myectomy. No reoperations were performed in any of these patients.

The symptoms resolved postoperatively in all patients. Patient 3 continued to have oscillopsia during the first three postoperative days. The oscillopsia disappeared on the fourth day and has not recurred. The resolution of the patient's symptoms correlated with the disappearance of the abnormal ocular movements seen on direct observation. None of the patients has reexperienced myokymia during the follow-up period.

Postoperatively, no patient had diplopia in primary gaze, although diplopia in lateral gaze (contralateral to the affected eye) or in downgaze was occasionally reported. The condition improved postoperatively in all patients.

Case Reports

Case 1

A 36-year-old woman developed intermittent oscillopsia and diplopia after a minor automobile accident. The patient was treated with diazepam by her family physician without benefit. The symptoms persisted for 18 months until she became pregnant. She was free of symptoms during her pregnancy, but the symptoms returned three months after delivery of her baby. She consulted one of us (C.S.H.) and treatment with carbamazepine was started. The carbamazepine relieved her symptoms, but because of dizziness and drowsiness, she discontinued the medicine ten months later. At this time she underwent superior oblique muscle tenotomy with immediate and complete relief of her symptoms. However, her operated-on eye developed overaction of the inferior oblique muscle with diplopia in its field of action and inferior oblique muscle myectomy was performed six months later. She has been free of all symptoms for more than 11 years.

Case 2

This 31-year-old woman developed intermittent oscillopsia that was most noticeable during knitting, sewing, and other manual craft activities. No preceding trauma or illness was associated with these symptoms. The problem was noted to disappear spontaneously for several months at a time, and the patient did not seek medical attention until two years later. Treatment with carbamazepine was started at that time and immediately relieved her symptoms. However, ten months later her oscillopsia returned and, despite an increased dose of carbamazepine, persisted unaffected. She therefore underwent superior oblique muscle tenotomy and inferior oblique muscle myectomy. On the first postoperative day, her symptoms had not improved. However, on the second postoperative day, she became free of symptoms and has remained so for nine years.

Case 3

A 25-year-old man was in a severe automobile accident that rendered him unconscious for 48 hours. He had a linear parietal fracture on the left side of his skull that was associated with a small subdural hematoma that was not surgically treated. Six weeks after his accident, he developed oscillopsia and diplopia in downgaze and sought medical consultation. He was treated with carbamazepine for three months without any improvement in his symptoms. He underwent superior oblique muscle tenotomy and inferior oblique muscle myectomy in his left eye. His symptoms persisted for three days postoperatively and then completely disappeared. He has remained free of symptoms for three years.

Case 4

A 32-year-old woman noted the gradual onset of oscillopsia and diplopia that was initially noted when she looked down at her speedome-

ter while driving. Her symptoms recurred sporadically with intermittent periods (several months) of remission. She did not seek medical attention until three years later. Her family physician thought the symptoms were secondary to stress and prescribed a minor tranquilizer that the patient did not take. Her symptoms became more persistent and one year later she sought consultation at our institution. Myokymia of the superior oblique muscle was diagnosed and treatment with carbamazepine was started. Initially, the patient thought the medical treatment reduced the symptoms, but after six months she discontinued the medication because she believed it was no longer effective. Surgical treatment was recommended, but she did not decide to undergo an operation until 14 months later. At that time, she had a superior oblique muscle tenotomy and an inferior oblique muscle myectomy performed on her left eye. She was immediately free of symptoms and has remained so for five months.

Discussion

In 1970, Hoyt and Keane[2] described a group of five patients with intermittent episodes of torsional diplopia and oscillopsia and named this entity superior oblique muscle myokymia. Since then, several studies on superior oblique muscle myokymia have been published. All have emphasized marked visual symptoms caused by rapid twitching of the superior oblique muscle.

Superior oblique muscle myokymia can have a variable course. Some patients have a spontaneous improvement or remission.[10] For symptomatic patients, several agents, including beta blockers,[8] benzodiazepines,[6,9] baclofen,[6,9] and phenytoin,[6,10] have been used with variable success. Carbamazepine has been the drug most commonly used,[6-8] despite potential side effects.[12]

For patients in whom the condition fails to improve with medication, or for those who cannot tolerate side effects, surgical treatment may be indicated. Ten patients have been described in published reports.[2,5,9,13-16] Palmer and Shults[13] described a series of three patients who were treated surgically (one patient had two operations; the other two had only one each) and observed that the condition improved in all three patients, but only one patient was completely satisfied. In 1970, Hoyt and Keane[2] treated one patient with one operation, and in 1973, Susac, Smith, and Schatz[5] treated one patient with one operation. The condition improved in both patients. In 1983, Keltner and associates[9] treated two patients with one operation each; the condition improved in one, but improved only temporarily in the other. In some studies, more than one operation per patient was required before an improvement resulted. In 1988, Ruttum and Harris[14] performed three operations in one patient; in 1986, Staudenmaier[15] performed two operations in one patient; and in 1980, Kommerell and Schaulbe[16] performed more than one operation in one patient.

In some cases, superior oblique muscle myokymia has recurred after superior oblique muscle tenctomy. The recurrence may be attributed to reattachment of the tendon to the globe[14] or the inability of the tendon to retract because of fibrillar attachments between the tendon, its sheath, and the globe.[17] Staudenmaier[15] advocates that tenectomy is more effective than tenotomy in these patients. Superior oblique muscle myectomy with trochlectomy has also been suggested as an alternative for recurrent superior oblique muscle myokymia.[14] Other patients have had symptoms caused by an iatrogenic superior oblique muscle palsy.[16] Many of these patients have undergone a second weakening procedure of the inferior oblique muscle.

We elected to perform tenotomy of the affected superior oblique muscle associated with weakening of the ipsilateral inferior oblique muscle (myectomy) in three of four patients. Our first patient underwent only a superior oblique muscle tenotomy. Diplopia caused by iatrogenic superior oblique muscle palsy developed, and an inferior oblique muscle myectomy performed six months later cured the diplopia. In three patients, we performed a simultaneous superior oblique muscle tenotomy combined with inferior oblique muscle myectomy with good results.

In Brown's syndrome, the decision to perform a simultaneous weakening procedure of the inferior oblique muscle with superior oblique muscle tenotomy has been debated.[18,19] In our experience with superior oblique muscle myokymia, the combined procedure has been effective and better than an isolated superior oblique muscle tenotomy, although the number of patients is limited. Oscillopsia resolved postoperatively in all our patients. Diplopia in lateral gaze or downgaze has been described after a combined superior oblique muscle/inferior

oblique muscle weakening procedure.[13,16] Diplopia in lateral gaze or downgaze was not a problem in our series, and none of the patients had diplopia in primary gaze.

Surgical treatment for superior oblique muscle myokymia should be reserved only for those patients in whom medical treatment fails or is intolerable. We believe that for this small group of patients, superior oblique muscle tenotomy combined with inferior oblique muscle myectomy was effective.

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Intraocular Fluid Cultures After Primary Pars Plana Vitrectomy

Steven M. Cohen, M.D., Jeffrey D. Benner, M.D., Maurice B. Landers III, M.D., and Lawrence S. Morse, M.D.

To determine what organisms enter the eye and remain in the eye after pars plana vitrectomy, vitreous cavity aspirates were cultured postoperatively. Two of 33 (6%) consecutive eyes undergoing primary pars plana vitrectomy had positive cultures. One sample grew a single colony of *Staphylococcus epidermidis*, the second grew two colonies of *Acinetobacter lwoffi*. Neither of these eyes developed endophthalmitis. This study demonstrates that bacteria enter the eye at a low rate during pars plana vitrectomy and that the eye on which a vitrectomy has been performed is capable of clearing a low inoculum of bacteria.

POSTOPERATIVE ENDOPHTHALMITIS often causes profound vision loss.[1,2] Recent reports showed that 29% to 43% of eyes undergoing uncomplicated cataract extraction with intraocular lens implantation have culture-positive anterior chamber aspirates at the conclusion of the operation.[3,4] Although no eyes in these studies developed endophthalmitis, other research has shown that bacteria introduced into the eye during an operation are the primary cause of postoperative endophthalmitis.[5]

Bacteria introduced into the anterior chamber are less able to cause a clinically important infection than bacteria introduced into the vitreous cavity.[6-9] Therefore, a small inoculum of bacteria entering the eye during pars plana vitrectomy might be more likely to cause endophthalmitis than a similar inoculum of bacteria entering the eye during cataract extraction. Additionally, vitrectomies often last several hours and involve many instrument insertions into the eye. The duration of the procedure and using several instruments might increase the risk of introducing bacteria into the eye during the procedure. To ascertain what organisms enter the eye during pars plana vitrectomy, we cultured intraocular fluid from eyes at the conclusion of pars plana vitrectomy.

Subjects and Methods

Thirty-three consecutive subjects undergoing primary pars plana vitrectomy at the University of California, Davis, Medical Center were included in the study. Patients were excluded if they had had penetrating trauma or a ruptured globe; had evidence of local or systemic infections at the time of surgery; or had previously undergone an anterior or posterior vitrectomy. The study was approved by the University of California, Davis, Human Subjects Review Committee.

The indications for vitrectomy were as follows: tractional macular detachments or vitreous hemorrhage from proliferative diabetic retinopathy (14 patients); rhegmatogenous retinal detachments with proliferative vitreoretinopathy (12 patients); submacular hemorrhage in age-related macular degeneration (two patients); ectopia lentis from Marfan's syndrome (two patients); vitreous hemorrhage in shaken infant syndrome (one patient); macular pucker (one patient); stage 5 retinopathy of prematurity (total retinal detachment) (one patient). The average age was 49 years. Of the 33 eyes undergoing surgery, 12 eyes had prior surgical procedures. Eight eyes were pseudophakic and one eye was aphakic.

All procedures were performed in the same operating room by two of us (L.S.M. or M.B.L.).

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From the Department of Ophthalmology, University of California, Davis, Sacramento, California (Drs. Cohen, Benner, and Morse); and Center for Retina and Vitreous Surgery, Memphis, Tennessee (Dr. Landers). This study was presented at the Association for Research in Vision and Ophthalmology Annual Meeting, Sarasota, Florida, May 6, 1992.

Reprint requests to Lawrence S. Morse, M.D., Department of Ophthalmology, University of California, Davis, 1603 Alhambra Blvd., Sacramento, CA 95816.

No preoperative antibiotics were administered. All patients underwent the following identical skin preparation. The eyelids and surrounding skin were scrubbed with 5% povidone-iodine in concentric rings outward from the eyelids for three minutes. The eyelashes were cleaned separately with povidone-iodine on cotton-tipped swabs. One or two drops of 5% povidone-iodine was placed in the conjunctival fornix. The skin was then blotted dry with a sterile gauze sponge. The eyelids were opened by the surgical assistant with the wood end of a cotton-tipped swab, and a clear plastic adhesive drape was placed over the eye. The drape was then incised over the globe and a wire eyelid speculum was used to tuck the edges of the drape around the eyelid margins and to maintain proper exposure.

A standard three-port pars plana vitrectomy was performed on each patient. Before closing the sclerotomies, or before the fluid-gas exchange, 0.3 to 0.7 ml of fluid was removed from the mid vitreous cavity with a blunt 20-gauge cannula into a sterile tuberculin syringe. The syringe was capped and taken to the adjacent microbiology laboratory. Under sterile conditions, the intraocular fluid was plated immediately on sheep-blood agar, chocolate agar, rose agar, MacConkey agar, and a drop was placed in thioglycolate broth. The first three plates were incubated at 35 C in 5% to 10% CO_2. The MacConkey agar and thioglycolate broth were incubated at35 C in ambient air. Any colonies located outside of the area plated with intraocular fluid were considered contaminants. If no organisms were seen, plates were discarded after three days, and the thioglycolate broth was discarded after seven days. Cultured organisms were identified both qualitatively and quantitatively by an experienced microbiologist.

Results

Only two of 33 samples (6%) of intraocular fluid from the vitreous cavity were culture-positive. One sample grew a single colony of *Staphylococcus epidermidis* on blood agar. Another sample grew two colonies of *Acinetobacter lwoffi* on chocolate agar.

The average time between the beginning of vitrectomy and the aspiration of fluid for the culture was 117 minutes. The elapsed time for the two patients with positive cultures was 100 and 120 minutes. Both of these patients were diabetic. One had had no previous operation and one was pseudophakic.

Discussion

Recent reports that 29% to 43% of eyes had culture-positive anterior chamber fluid after routine cataract extraction suggest that contemporary ophthalmic operation is not absolutely sterile.[3,4] In our patients, only two of 33 (6%) eyes had culture-positive intraocular fluid after vitrectomy. Each positive culture grew only one or two colonies of bacteria.

Endophthalmitis after pars plana vitrectomy is rare, with an incidence of 0.05% to 0.14%.[10-17] In a survey of 30,002 cases, Kattan and associates[10] found the incidence of endophthalmitis after pars plana vitrectomy comparable to that after cataract extraction.[10] Despite the similar rates of endophthalmitis after cataract extraction, only 6% of eyes had culture-positive intraocular fluid after pars plana vitrectomy, compared to 29% to 43% of eyes that were culture-positive after cataract extraction.[3,4] Thus, even though bacteria remain in the eye much less often after pars plana vitrectomy than after cataract extraction, those bacteria that enter the vitreous cavity during vitrectomy may have a greater chance of producing endophthalmitis.

There are at least two possible reasons why bacteria would have a greater chance of causing endophthalmitis once they gain access to the vitreous cavity. First, animal studies have demonstrated that in vivo, the vitreous is a better culture medium than the aqueous humor. In 1955, Maylath and Leopold[6] showed that the anterior chamber of rabbits was better able to overcome infections with small numbers of bacteria than the vitreous. This finding has been supported by human studies demonstrating that a communication with the vitreous cavity during anterior segment procedures confers a much greater risk of postoperative endophthalmitis.[7-9,17] Secondly, both gentamicin and cephalosporins injected subconjunctivally do not penetrate well into the vitreous cavity.[18,19] Therefore, subconjunctival injections administered postoperatively would be more effective at eradicating intraocular bacteria after an anterior segment procedure than after posterior segment cataract extraction.

Although not as efficient as the anterior

chamber, the vitreous is capable of overcoming invading bacteria. In an intact eye, the vitreous is able to kill bacteria through inflammatory-related mechanisms.[20,21] Additionally, although the vitreous is an excellent culture medium for bacteria, invading bacteria probably do not survive and multiply as well in the balanced salt solution remaining in the eye after pars plana vitrectomy.

The lower incidence of culture-positive intraocular fluid found in our patients is probably attributable to differences in surgical technique between pars plana vitrectomy and cataract extraction. Pars plana vitrectomy is performed through several small incisions. The small incisions may help prevent bacteria from entering the eye. Sherwood and associates[4] showed that during cataract extraction, fluid is drawn into the eye during aspiration of the lens cortex and during intraocular lens insertion. During pars plana vitrectomy a continuous infusion of solution maintains positive pressure within the globe. The constant pressure causes an outflow of fluid when incisions are made and whenever instruments are removed from the eye. This outward flux of irrigating solution during pars plana vitrectomy may prevent bacteria from entering the eye. Furthermore, the flow of solution through the eye may remove most bacteria that gain entry.

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Criteria to Detect Minimal Expressivity Within Families With Autosomal Dominant Aniridia

Helen A. Mintz-Hittner, M.D., Robert E. Ferrell, Ph.D., Leslie A. Lyons, Ph.D., and Frank L. Kretzer, Ph.D.

Autosomal dominant aniridia with complete penetrance without Wilms' tumor in five generations with 27 affected family members has been reassigned from chromosome 2p25 to chromosome 11p13. Clinically, aniridia was obvious in affected individuals with variable expressivity when they had rudimentary iris stumps, typical or atypical iris colobomata, or round, eccentric pupils. However, iris and retinal fluorescein angiography was required to detect abnormal vascular remodeling that resulted in incomplete iris collarettes and decreased retinal foveal avascular zones in 27 family members at risk with round, central pupils. These angiograms distinguished five affected and 22 unaffected individuals, and were the critical criteria required to detect minimal expressivity of aniridia in family members with round, central pupils.

AUTOSOMAL DOMINANT ANIRIDIA associated with Wilms' tumor, genitourinary anomalies, and mental retardation has been localized definitively to chromosome 11p13.[1] In 1980, linkage analysis of a single family with autosomal dominant aniridia without Wilms' tumor gave a preliminary assignment of the aniridia gene to chromosome 2p25.[2] Recently, a panel of restriction fragment length polymorphisms[3] has been used to reassign this gene to chromosome 11p13.[4]

Clinically, affected individuals in this family with aniridia were obvious when they had rudimentary iris stumps, typical or atypical iris colobomata, or round, eccentric pupils.[5] However, designation of disease status in individuals with round, central pupils was problematic. We defined the iris and retinal fluorescein angiographic criteria to detect minimal expressivity within such families.

Patients and Methods

Twenty-six individuals in five generations of a single family were shown by examination to have aniridia, and aniridia was ascertained in one individual (I-1) by review of ophthalmic records (Fig. 1). Of these 27 patients, five had rudimentary iris stumps, eight had typical or atypical iris colobomata, nine had round, eccentric pupils, and five had round, central pupils. Additionally, 33 presumed unaffected relatives (22 at risk and 11 not at risk) were examined. Clinical photographs of the undilated irides were taken at the time of initial examination of all family members (before 1980) and again at the time of this second examination. Clinical fundus photographs of the macular reflex were taken of all family members through the dilated irides at the time of the examinations. Twenty-seven individuals at risk with round, central pupils underwent fundus fluorescein angiography to evaluate the foveal avascular zone of one eye, followed by iris fluorescein angiography to appraise the collarette of the fellow eye. Two masked observ-

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From the Departments of Ophthalmology (Drs. Mintz-Hittner and Kretzer), Pediatrics (Dr. Mintz-Hittner), and Cell Biology (Dr. Kretzer), Baylor College of Medicine, Houston, Texas; and the Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania (Drs. Ferrell and Lyons). This study was presented in part at the American Association for Pediatric Ophthalmology and Strabismus Annual Meeting, Maui, Hawaii, Feb. 13, 1992. This study was supported in part by grants from Research to Prevent Blindness, Inc., New York, New York; and the National Eye Institute.

Reprint requests to Frank L. Kretzer, Ph.D., Cullen Eye Institute, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030.

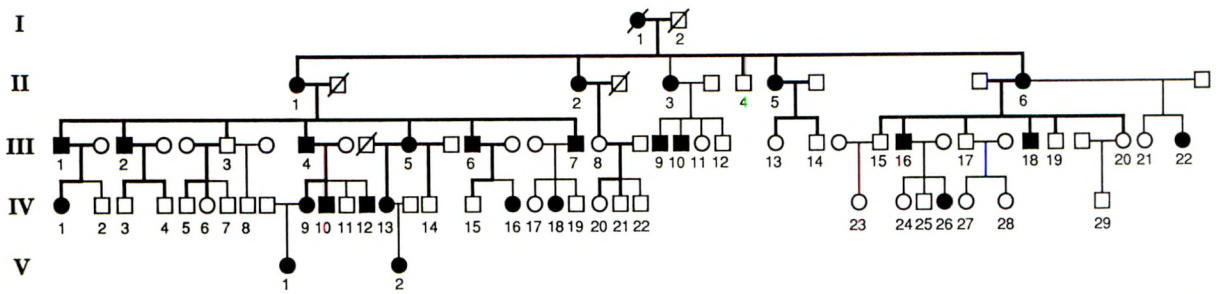


Fig. 1 (Mintz-Hittner and associates). Pedigree of kindred segregating for autosomal dominant aniridia with complete penetrance and variable expressivity. The thick lines delineate the family members previously studied in 1980.[2,5] The thin lines indicate the additional family members studied in 1992.[4] The single patient in whom a misdiagnosis was made in 1980 is IV-10.

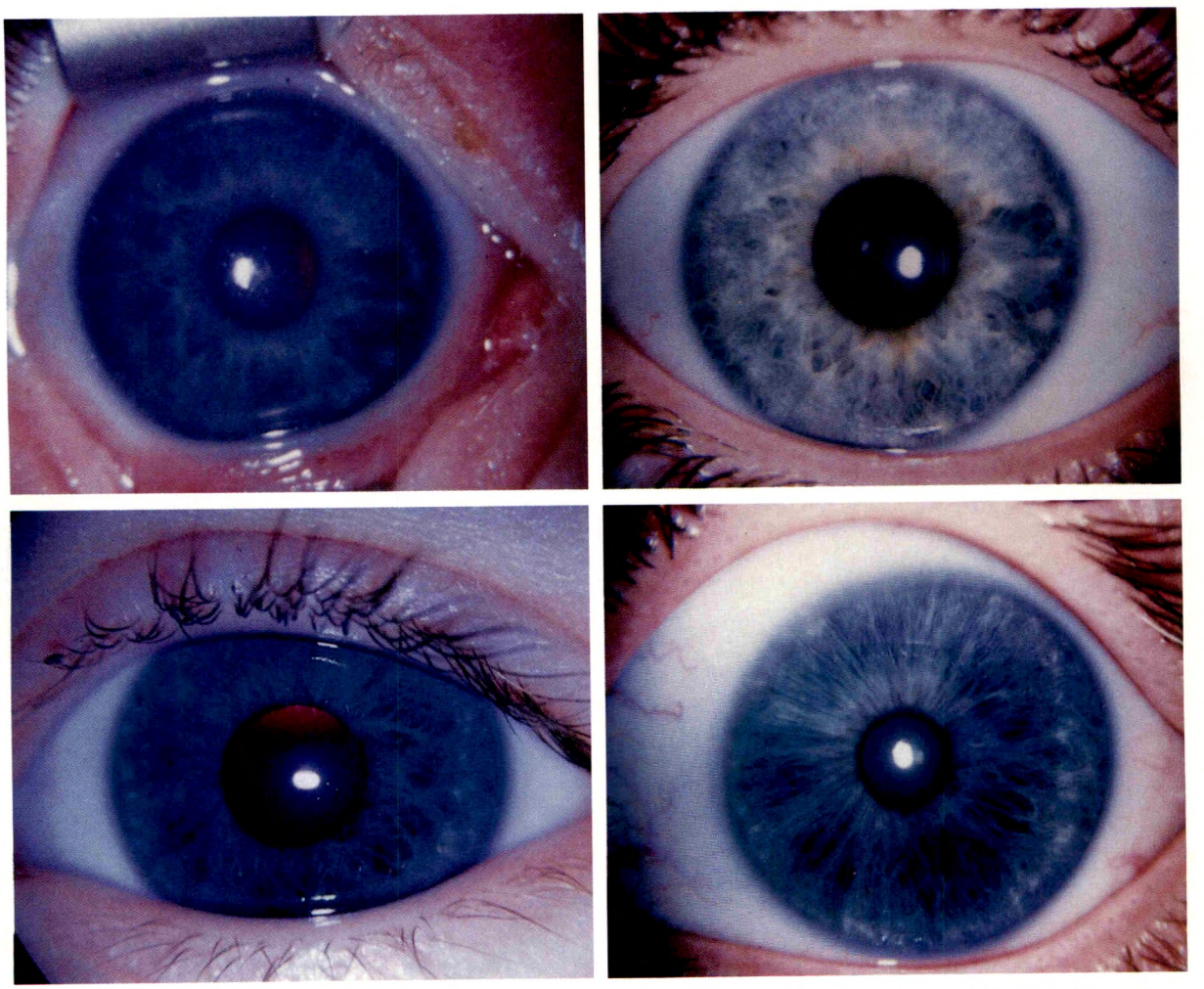


Fig. 2 (Mintz-Hittner and associates). Clinical photographs of immature (less than 1 year old) and mature (one decade later) blue irides. Top left, Unaffected immature iris with thin iris stroma (IV-15). Top right, Unaffected mature iris with collarette and thick iris stroma (IV-15). Bottom left, Affected immature iris with thin iris stroma (IV-10) (incorrectly designated in 1980[2,5]). Bottom right, Affected mature iris with absent iris collarette and thin iris stroma (IV-10).

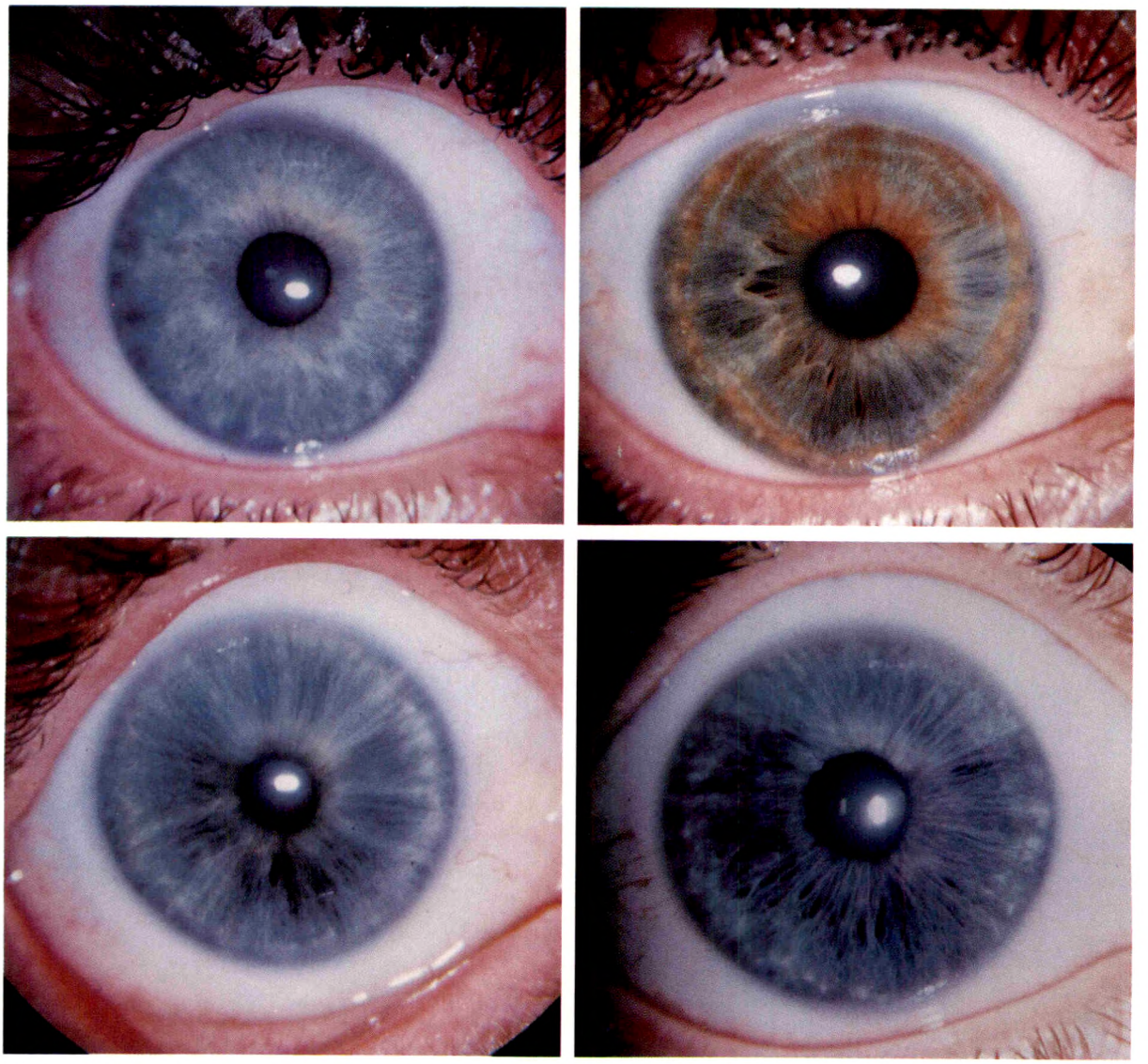


Fig. 3 (Mintz-Hittner and associates). Clinical photographs of mature irides. Top left, Unaffected individual with normal iris collarette and thick blue iris stroma (III-15). Top right, Affected individual with partial iris collarette and thin brown iris stroma (III-6). Bottom left and right, Affected individual with absent iris collarette and thin blue iris stroma (III-4 and IV-10, respectively).

ers uniformly designated these angiograms as either normal or abnormal.

Results

The family pedigree (Fig. 1) showed the segregation of aniridia to be consistent with autosomal dominant inheritance with complete penetrance. Of the 27 affected members, 16 were females and 11 were males. Of the 48 individuals at risk, 26 (54.2%) were affected. There was extreme variability in the appearance of the irides of the affected members from rudimentary iris stumps to iris thinning with round, central pupils, which is characteristic of variable expressivity.[5] Twenty-seven individuals with round, central pupils were at risk. Five of these individuals were affected, and 22 were normal according to iris and retinal fluorescein angiographic criteria.

We compared the appearance of the iris of an unaffected member (Fig. 2, top left and right)

and of an affected member (Fig. 2, bottom left and right) in this pedigree during the first year of life (immature iris, Fig. 2, top and bottom left), and one decade later (mature iris, Fig. 2, top and bottom right). Slit-lamp examination disclosed transillumination of the iris in both unaffected and affected immature family members and no transillumination of the iris in both unaffected and affected mature family members.

In the pedigree, the appearance of round, central pupils at maturity varied from normal with an almost complete iris collarette in an unaffected member (Fig. 3, top left), to iris thinning with a questionable iris collarette in an affected member (Fig. 3, top right), to iris thinning with an absent iris collarette in affected members (Fig. 3, bottom left and right). Slit-lamp examination disclosed normal iris crypts on both sides of the iris collarette in unaffected members, and iris crypts between the pupillary border and the base of the iris in affected members.

Iris fluorescein angiography demonstrated an almost complete iris collarette in an unaffected member (Fig. 4, top left), the difficulties in detecting the presence or absence of a collarette in a brown iris in an affected member (Fig. 4,

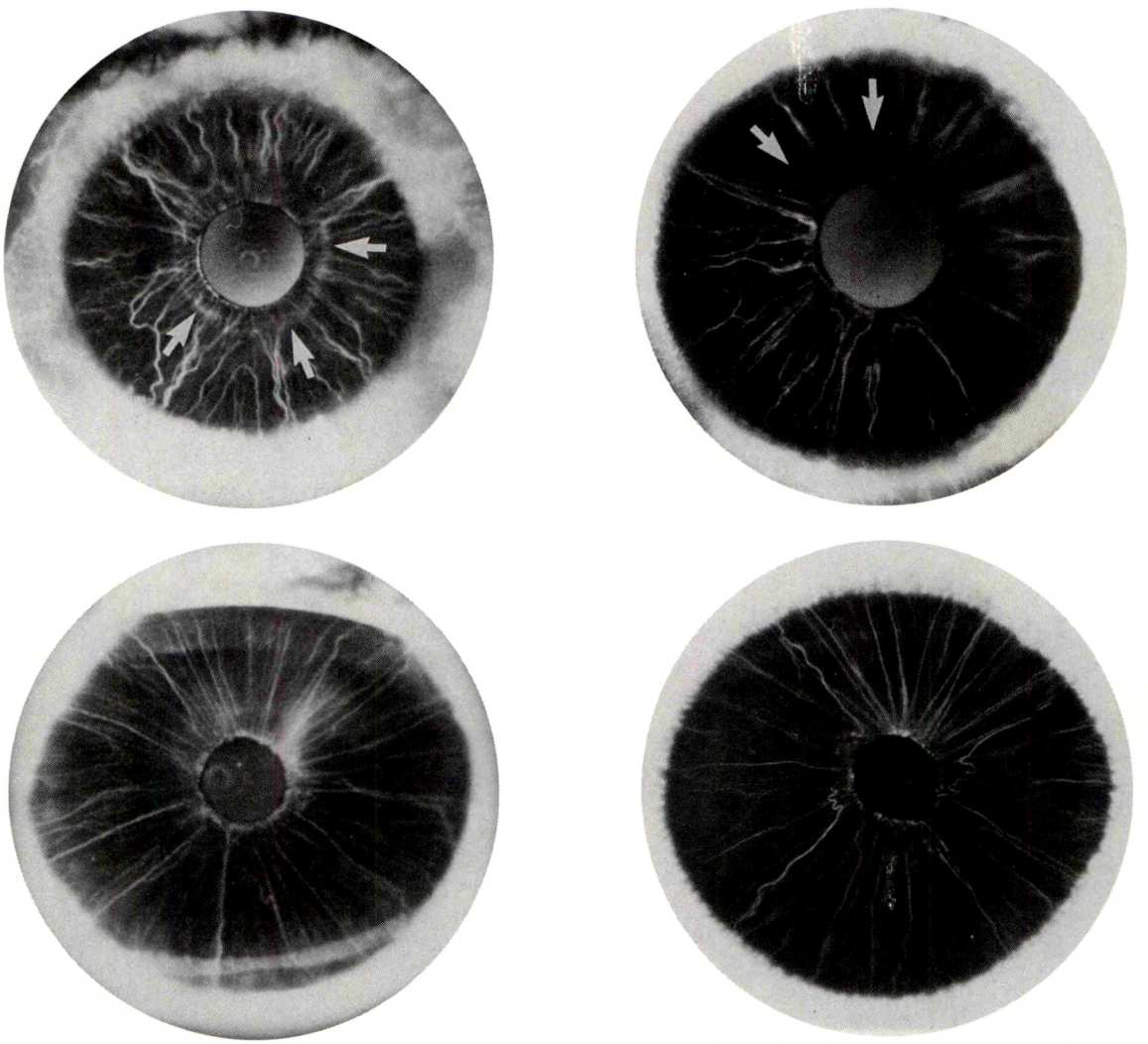


Fig. 4 (Mintz-Hittner and associates). Fluorescein angiograms of mature irides of the same eyes of the same patients as in Figure 3. Top left, Normal iris collarette apparent through thick blue iris stroma (arrows) (III-15). Top right, Iris collarette concealed by thin brown iris stroma (arrows) (III-6). Bottom left and right, Absent iris collarette (III-4 and IV-10).

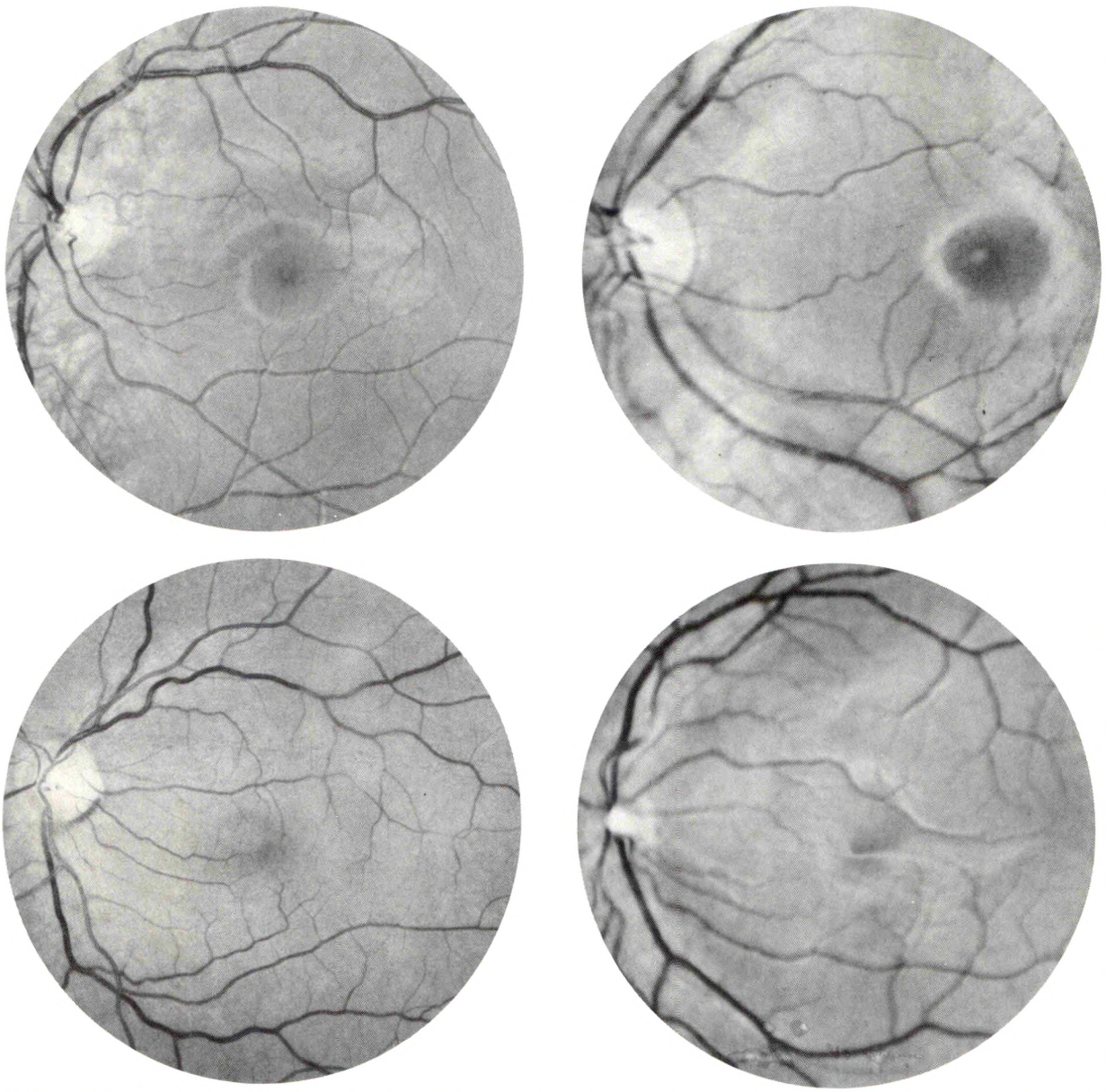


Fig. 5 (Mintz-Hittner and associates). Clinical photographs of mature fundi. Top left, Unaffected individual with normal macular reflex (IV-11). Top right, Affected individual with normal macular reflex (III-7). Bottom left, Affected individual with moderately decreased macular reflex (III-6). Bottom right, Affected individual with markedly decreased macular reflex (IV-10).

top right), and the absence of an iris collarette in affected members (Fig. 4, bottom left and right).

In the pedigree, the appearance of the macular reflex varied from normal in an unaffected member (Fig. 5, top left) and in an affected member (Fig. 5, top right), to moderately diminished in an affected member (Fig. 5, bottom left), to markedly diminished in an affected member (Fig. 5, bottom right).

Retinal fluorescein angiography was required to demonstrate the size of the foveal avascular zone from normal in an unaffected member (Fig. 6, top left) to markedly diminished in all affected members (Fig. 6, top right, bottom left and right).

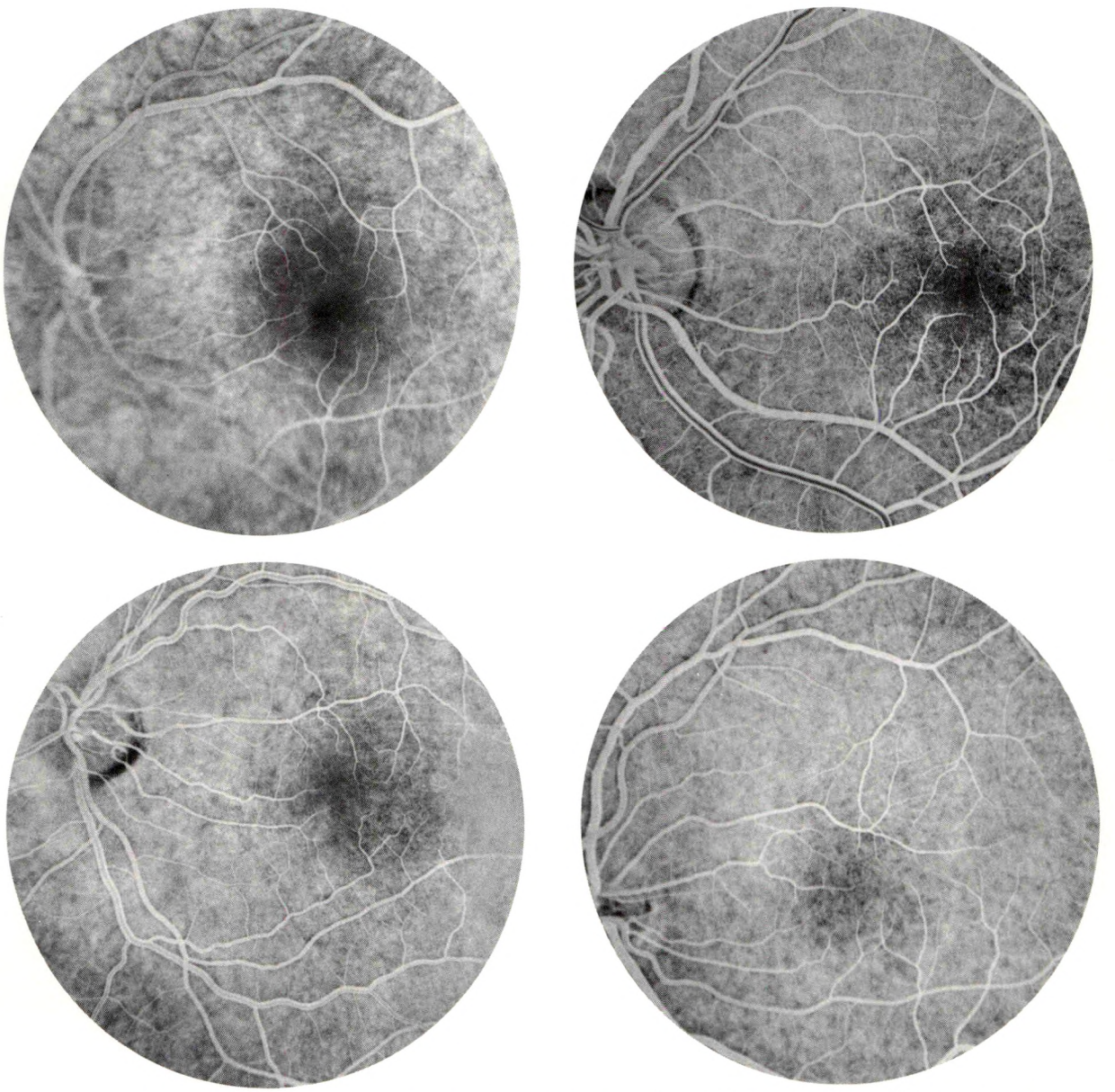


Fig. 6 (Mintz-Hittner and associates). Fluorescein angiograms of fundi of the same eyes of the same patients as in Figure 5. Top left, Normal foveal avascular zone (IV-11). Top right, bottom left and right, Reduced foveal avascular zones (III-7, III-6, and IV-10, respectively).

In all five affected individuals at risk with round, central pupils (III-4, III-6, III-7, IV-10, and IV-16), both iris and retinal fluorescein angiograms were abnormal.

Discussion

The normal iris has a circular collarette approximately 2 mm from the pupillary margin that divides the iris into two zones, a narrow pupillary zone and a wider ciliary zone. Embryologically, the annular vessel (at the pupillary margin of the iris) arises from the hyaloid artery and sends radial vessels toward the base of the iris (by the seventh week of gestation). The major arterial circle (near the iris root, in the stroma of the ciliary body) arises from the long posterior ciliary arteries and sends radial vessels toward the pupil (by the 24th week of gestation). These radial vessels form the pupil-

lary membrane. In the region of the collarette (the thickest portion of the iris), anastomoses occur between the arterial and venous arcades (by the 32nd week of gestation); however, a true minor iris circle (collarette) does not exist. With development, the annular vessel and the radial vessels entering the minor iris circle atrophy, leaving the narrow pupillary zone relatively avascular (by the 32nd week of gestation). The wide ciliary zone remains highly vascular.[6]

During the first year of life, when the irides were immature, it was impossible to assign disease status by iris photography (Fig. 2) or by iris transillumination alone. Stromal density and melanocyte pigmentation as well as posterior epithelial pigmentation increase during the first year of life. Thus, in both unaffected and affected members, immature irides have an indistinct collarette and appear thin and transilluminate. It was at this age that detection of minimal expressivity within this family was problematic.

Normal minor arterial circles (collarettes) did not form in affected individuals with round, central pupils in this family because the annular vessel with its radial projections failed to atrophy (remodel). Thus, affected members had markedly reduced (Fig. 3, top right) or absent (Fig. 3, bottom left and right) iris collarettes.

In individuals with round, central pupils, iris fluorescein angiography can provide a critical criterion to detect minimal expressivity in families with aniridia: an incomplete or absent iris collarette. This supplements the traditional definition of aniridia in terms of irregularities of the location or configuration of the pupillary margin. However, iris fluorescein angiography may be inconclusive because normal individuals have an incomplete minor arterial circle (Fig. 4, top left). Furthermore, examination will not disclose this minor arterial circle in individuals with brown irides (Fig. 4, top right) because the iris stroma is thickest at this point and obscures the collarette. Thus, retinal fluorescein angiography must be used in conjunction with iris fluorescein angiography to confirm unaffected members with partial collarettes in blue irides and to determine affected members with obscure collarettes in brown irides.

The normal macular reflex is delineated by the beginning of the slope at the thickest portion of retina (1,500-μm diameter). The fovea is the avascular zone (300- to 500-μm diameter) with lateral displacement of inner retinal layers.[7] Unlike the iris, the clinical appearance of the macular reflex and of the retinal fluorescein angiogram of the foveal avascular zone are present at birth in term infants.

Normal foveal avascular zone did not form in affected individuals with round, central pupils in this family because the inner retinal vessels in the macular region failed to atrophy (remodel). However, irrespective of disease status, the macular reflex could appear normal in unaffected members (Fig. 5, top left) and in affected members (Fig. 5, top right).

In individuals with round, central pupils, fundus fluorescein angiography can provide a second critical criterion to detect minimal expressivity in families with aniridia: a reduced or absent foveal avascular zone. Thus, unaffected members uniformly had normal foveal avascular zones (Fig. 6, top left), and affected members uniformly had diminished or absent foveal avascular zones (Fig. 6, top right, bottom left and right) regardless of the presence of a normal macular reflex (Fig. 5, top right) or a reduced macular reflex (Fig. 5, bottom left and right).

Thus, minimal expressivity of aniridia is reflected in vascular elements that overlay specialized neuroectodermal regions that failed to atrophy (remodel). This abnormal vascular remodeling in the iris results in the absence of a collarette. This abnormal vascular remodeling in the retina results in the absence of a foveal avascular zone. Both of these vascular atrophies must be neuroectodermally induced.[8]

In 1980, affected individuals with round, central pupils were noted to have abnormal vascular loops and leakage of dye demonstrated by iris fluorescein angiography.[5] All affected individuals were noted to have abnormal foveal avascular zones demonstrated by fundus fluorescein angiography.[5] However, the absence of the iris collarette was not perceived, and iris and fundus fluorescein angiography was not performed uniformly on all patients at risk with round, central pupils. Thus, the lack of an understanding of these two critical criteria in detecting minimal expressivity led to the erroneous designation of one young affected individual as normal (IV-10) (Fig. 2, bottom; Figs. 3 through 6, bottom right). This then led to the erroneous assignment of linkage of autosomal dominant aniridia with complete penetrance but variable expressivity without Wilms' tumor to chromosome 2p25[2] rather than to chromosome 11p13.[4]

The disease status of one patient (IV-10) was questioned only when the family was restudied and linkage to 11p13 was suggested by a new panel of restriction fragment length polymor-

phisms.[8] Only then were all 27 of the individuals at risk with round, central pupils reexamined with fluorescein angiography to appraise the collarette of the iris and the foveal avascular zone of the retina. Five individuals were found to have both abnormal iris and retinal fluorescein angiograms and to have aniridia linked to chromosome 11p13.

All families with autosomal dominant aniridia can now be restudied with fluorescein angiography to designate clinical status in individuals with round, central pupils. A compilation of multiple families with aniridia will assist in the proper ordering of the polymorphisms along the chromosome band 11p13.

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OPHTHALMIC MINIATURE

Cathy walked into the bathroom and looked at herself in the mirror. Okay, she wasn't a pink-cheeked kid anymore. There were worry lines around her mouth and squint lines around her eyes. She should have her spectacle prescription looked at. She was starting to get headaches during procedures, and she knew it could be a problem with her eyes—she was, after all, an ophthalmic surgeon—but like everyone else she was short of time and was putting off having her eyes looked at by another member of The Wilmer Eye Institute staff. At least the color didn't change, even though their refractive error might suffer from all the close work that her job mandated.

Tom Clancy, *The Sum of All Fears*
New York, G. P. Putnam's Sons, 1991, p. 454

Causes of Reduced Visual Acuity on Long-term Follow-up After Cataract Extraction in Patients With Uveitis and Juvenile Rheumatoid Arthritis

Gregory M. Fox, M.D., Harry W. Flynn, Jr., M.D., Janet L. Davis, M.D., and William Culbertson, M.D.

We reviewed the long-term follow-up on a consecutive series of 16 eyes from ten patients with juvenile rheumatoid arthritis–associated cataracts that were removed by using pars plana lensectomy and vitrectomy. All patients had prominent cataracts, chronic uveitis, posterior synechiae, and vitreitis preoperatively, and had at least 12 months of follow-up postoperatively. The median length of follow-up was 51 months (range, 12 months to ten years). In the early postoperative period, a visual acuity of 20/70 or better was obtained in 13 of 16 eyes (81%). With longer follow-up, the final visual acuity was 20/70 or better in only nine of 16 eyes (56%). The primary categories of delayed visual loss in these cases were glaucoma and macular disease (chronic cystoid macular edema, macular hole, hypotony maculopathy, and recurrent macular pucker). Despite these limitations in maintaining good visual acuity, a pars plana lensectomy and vitrectomy approach is effective for cataracts in these patients with uveitis.

Chronic uveitis and cataracts develop commonly in patients with juvenile rheumatoid arthritis.[1] It has been proposed that cataracts form in these patients because of the uveitis and also secondary to long-term corticosteroid treatment.[1-6] Cataract extraction in these patients by using either intracapsular methods or discission and aspiration has been fraught with many complications, including a high incidence of phthisis bulbi.[7,8] More recently, better visual acuity results have been found in these cases with automated vitrectomy instruments by using either a limbal or pars plana approach.[9-12] Good results have also been found after phacoemulsification.[13] With the exception of the study by Kanski,[12] the length of follow-up in these series has been somewhat limited in these patients, who often require a cataract extraction at a young age. We studied the results of long-term follow-up in patients with juvenile rheumatoid arthritis and uveitis in whom cataracts were removed by using a pars plana lensectomy and vitrectomy approach. We focused on the causes of reduced final visual acuity on long-term follow-up postoperatively.

Patients and Methods

We reviewed a consecutive series of 16 eyes from ten patients with juvenile rheumatoid arthritis–associated cataracts that were removed by using pars plana lensectomy and vitrectomy, and had at least 12 months of follow-up. There were eight females and two males. The average age of the patients at the time of surgery was 19 years (range, 6 to 45 years). The median duration of follow-up of these patients was 51 months (range, 12 months to ten years).

The medical charts were reviewed to obtain the following information: (1) clinical characteristics of the systemic disease; (2) preoperative characteristics (Table 1), including the presence of anterior chamber inflammation, increased intraocular pressure, band keratopathy, and in a few cases in which the cataract permitted a sufficient view of the posterior fundus, the presence of cystoid macular edema or optic atrophy; and (3) intraoperative findings

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From the Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami School of Medicine, Miami, Florida.

Reprint requests to Harry W. Flynn, Jr., M.D., Bascom Palmer Eye Institute, P.O. Box 016880, Miami, FL 33101.

TABLE 1
PREOPERATIVE AND OBSERVED INTRAOPERATIVE OCULAR CHARACTERISTICS

PATIENT NO., GENDER, AGE (YRS)	EYE	PREOPERATIVE VISUAL ACUITY	INTRAOCULAR PRESSURE (MM HG)	PREOPERATIVE MEDICATIONS	ANTERIOR CHAMBER REACTION	OTHER OCULAR CONDITIONS
1, F, 24	L.E.	20/100	14	None	Mild cells, marked flare	Severe myopia, band keratopathy
2, F, 11	R.E.	Hand motions	24	Topical corticosteroids, cycloplegic	No cells, mild flare	None
	L.E.	5/200	16	Same	Mild cells, mild flare	Macular cyst or hole, band keratopathy
3, F, 45	R.E	4/200	13	Systemic and topical corticosteroids	Trace cells, mild flare	Band keratopathy
	L.E.	20/200	15	Same	Mild cells, mild flare	Band keratopathy
4, F, 6	R.E.	20/200	17	Topical corticosteroids, cycloplegic	Moderate cells, mild flare	Amblyopia, exotropia, epiretinal membrane
5, M, 16	R.E.	Hand motions	22	Carbonic anhydrase inhibitor, beta-blocker	Trace cells, trace flare	Glaucoma
	L.E.	20/60	32	Same	Trace cells, marked flare	Glaucoma
6, F, 14	R.E.	20/300	14	Systemic corticosteroids, cycloplegic	Moderate cells, mild flare	Band keratopathy, status-post chelation
	L.E.	4/200	17	Same	No cells, moderate flare	Band keratopathy, status-post chelation
7, F, 15	R.E.	20/400	27	Carbonic anhydrase inhibitor, beta-blocker	Trace cells, no flare	Glaucoma, severe myopia
	L.E.	2/200	13	Same	No cells, moderate flare	Glaucoma, severe myopia
8, F, 25	L.E.	9/200	9	Topical corticosteroids	Trace cells, moderate flare	None
9, M, 13	R.E.	Counting fingers	12	Topical and systemic corticosteroids	No cells, mild flare	None
10, F, 21	R.E.	Hand motions	9	Beta-blocker, dipivefrin hydrochloride	No cells, no flare	Chronic glaucoma
	L.E.	10/200	17	Topical corticosteroids	No cells, no flare	None

(Table 1), including the amount of vitreous opacification, the status of the posterior hyaloid, and the presence of cystoid macular edema or glaucomatous optic nerve damage. Long-term follow-up, including visual acuity, intraocular pressure, ocular medications, and a description of fundus details on most recent follow-up was obtained either on examination by one of us or by contacting the referring ophthalmologist.

The preoperative visual acuity ranged from 20/100 to hand motions. A posterior subcapsular cataract was the most common type of cataract in these patients. Posterior synechiae extending from 180 to 360 degrees of the pupillary circumference were present in all cases. The cataract precluded adequate examination of the macula in most cases, but the cystoid macular edema was definitely described at the time of surgery in seven eyes. In two eyes with less dense cataracts, cystoid macular edema was confirmed preoperatively by fluorescein angiography (Table 1, Case 1, left eye; and Case 3, left eye).

No standardized protocol for preoperative treatment of intraocular inflammation was used in this series. At the time of surgery, patients had variable cellular reaction in the anterior chamber. This anterior chamber reaction ranged from none to moderate (Table 1). No patients underwent surgery during acute episodes of anterior uveitis. All patients had observed cellular reaction in the vitreous preoperatively or at the time of the pars plana vitrectomy. Most patients were being treated with topical corticosteroids and cycloplegic agents preoperatively. These topical medications were not increased in an attempt to reduce

preoperative inflammation. Two patients were being treated by their referring physicians with methylprednisolone, 2 to 4 mg daily (Table 1, Case 1, left eye; and Case 3, left eye). One patient was treated for three days with prednisone, 40 mg daily, immediately before lensectomy and vitrectomy (Table 1, Case 9). Otherwise, these patients were not routinely treated with systemic corticosteroids before their ocular surgery.

The surgical technique used in these cases has been previously described in detail.[9] In brief, a standard pars plana lensectomy and vitrectomy approach was used in all cases. A bent needle was used as a secondary infusion cannula until a clear view of the pars plana infusion cannula was present. The lens nucleus was usually removed by aspiration and cutting with a standard 20-gauge vitrectomy instrument, but occasionally ultrasound fragmentation was used for nucleus removal. Scleral depression over the ciliary body was performed to permit safe removal of all peripheral lens capsule and cortex adjacent to the ciliary body. Subsequently, a posterior vitrectomy was performed.

At the time of vitrectomy, a posterior vitreous detachment was noted in six eyes (Table 1, Case 3, both eyes; Case 4, right eye; Case 8, left eye; Case 9, right eye; and Case 10, left eye). A posterior vitreous detachment was created surgically in four eyes (Table 1, Case 1, left eye; Case 5, left eye; and Case 7, both eyes). The posterior hyaloid was noted to be firmly adhered to the retina and was not surgically removed in five eyes (Table 1, Case 2, both eyes; Case 5, right eye; and Case 6, both eyes). The status of the posterior hyaloid at the time of surgery was not described in the operative report of one eye (Table 1, Case 10, right eye).

No routine postoperative treatment regimen was used in this series. Subconjunctival injections of triamcinolone acetonide (20 mg) and dexamethasone (2 to 12 mg) were administered, together with antibiotics at the end of surgery. Topical corticosteroids and cycloplegics with varying treatment schedules were used in all patients.

Results

The visual acuity improved in all patients in the early postoperative period. A visual acuity of 20/70 or better was obtained in 13 of 16 eyes (81%), and the remaining three of 16 eyes (19%) had a visual acuity of 20/100 to 20/200 during the first six months of follow-up (Table 2). With longer follow-up (median, 51 months), the final visual acuity was 20/70 or better in only nine of 16 eyes (56%). A visual acuity of 20/80 to 20/200 was maintained in five of 16 eyes (31%), and two of 16 eyes (13%) had poor visual acuities of 4/200 and 20/300.

Low intraocular pressure ranged from 2 to 6 mm Hg for one to three weeks postoperatively in six eyes (Table 2). A nonhemorrhagic choroidal detachment developed in one hypotonous eye (Table 2, Case 7, left eye), but resolved within two weeks of surgery. Prolonged hypotony (intraocular pressure less than 6 mm Hg) lasting from three to seven months occurred in two eyes (Table 2, Case 5, right eye; and Case 9, right eye). One eye also had a mild postoperative vitreous hemorrhage that resolved without intervention (Table 2, Case 9, right eye).

Retinal detachment did not occur in any eye postoperatively. One eye had an increased intraocular pressure of 40 mm Hg that lasted for one day (Table 2, Case 4, right eye). Despite mild band keratopathy near the corneoscleral limbus in most eyes, this keratopathy was not noted to progress during the follow-up course. One patient had an iatrogenic retinal tear intraoperatively during removal of the posterior cortical vitreous. This break was treated with endolaser photocoagulation and fluid-gas exchange. No complications from this break were observed during follow-up (Table 2, Case 5, left eye). Of those patients in whom the posterior cortical vitreous was not removed, none developed opacification of the residual vitreous. Most patients continued to have a variable, low-grade intraocular cellular reaction on long-term follow-up.

Three eyes with glaucoma preoperatively developed loss of visual acuity postoperatively because of complications of chronic glaucoma. Despite two trabeculectomies, the visual acuity in one eye decreased from 20/40 at 20 months postoperatively to 20/300 ten years postoperatively (Table 2, Case 5, right eye) because of advanced glaucomatous cupping of the optic nerve head. This patient's fellow eye had a visual acuity of 20/25 six months after lensectomy and vitrectomy, and at the last follow-up visit 12 months postoperatively, the visual acuity had decreased to 20/50 on the basis of further glaucomatous optic nerve damage (Table 2, Case 5, left eye). This patient has refused filtration surgery for the left eye. Another pa-

TABLE 2
VISUAL ACUITY RESULTS AND LENGTH OF FOLLOW-UP

			POSTOPERATIVE VISUAL ACUITIES				POSTOPERATIVE COMPLICATIONS	
PATIENT NO.	EYE	PREOPERATIVE VISUAL ACUITY	BEST VISUAL ACUITY DURING FOLLOW-UP	FOLLOW-UP (MOS)	FINAL VISUAL ACUITY	FOLLOW-UP (MOS)	EARLY	LATE
1	L.E.	20/100	20/30	(57)	20/30	(57)	Transient hypotony with choroidal folds (2 wks)	None
2	R.E.	Hand motions	20/30	(31)	20/30	(31)	None	Glaucoma
	L.E.	5/200	20/200	(30)	20/200	(30)	None	Glaucoma, macular hole from chronic macular edema
3	R.E.	4/200	20/20	(15)	20/40	(51)	Transient hypotony (1 wk)	Chronic cystoid macular edema
	L.E.	20/200	20/20	(14)	20/70	(45)	Transient hypotony (1 wk)	Chronic cystoid macular edema
4	R.E.	20/200	20/60	(6)	20/200	(87)	Fibrin pupillary membrane	Recurrent epiretinal membrane involving macula, amblyopia
5	R.E.	Hand motions	20/40	(20)	20/300	(122)	Prolonged hypotony (7 mos)	Glaucoma with visual loss despite trabeculectomy
	L.E.	20/60	20/25	(6)	20/50	(12)	None	Glaucoma with visual loss (patient refuses further surgery)
6	R.E.	20/300	20/25	(57)	20/25	(57)	None	Increased intraocular pressure without visual field loss
	L.E.	4/200	20/25	(54)	20/25	(54)	None	Increased intraocular pressure without visual field loss
7	R.E.	20/400	20/30	(12)	4/200	(70)	Transient hypotony, choroidal detachment (2 wks)	Chronic hypotony with macular folds after Molteno implantation
	L.E.	2/200	20/30	(16)	20/50	(65)	None	Chronic glaucoma, trabeculectomy performed
8	L.E.	9/200	20/20	(51)	20/20	(51)	Transient hypotony (2 wks)	Increased intraocular pressure without visual field loss
9	R.E.	Counting fingers	20/200	(15)	20/200	(15)	Prolonged hypotony and macular folds (3 mos), mild vitreous hemorrhage	Chronic cystoid macular edema
10	R.E.	Hand motions	20/100	(19)	20/100	(19)	None	Chronic cystoid macular edema
	L.E.	10/200	20/70	(6)	20/80	(18)	Transient hypotony (1 wk)	Chronic cystoid macular edema

tient underwent the following two separate glaucoma treatment procedures: (1) a YAG laser cyclodestructive procedure, and (2) a Molteno implantation. This eye became chronically hypotonous after the Molteno implantation and developed prominent retinal folds in the macula, which resulted in a visual acuity of 4/200 (Table 2, Case 7, right eye). Of two additional eyes with preoperative glaucoma, one eye required no change in glaucoma medications, and one eye had a trabeculectomy with mitomycin C five years after lensectomy and vitrectomy (Table 2, Case 7, left eye). Finally, five eyes with no evidence of glaucoma before cataract extraction developed moderately increased intraocular pressures postoperatively (less than 35 mm Hg). Two of these five eyes are being treated with a topical beta-blocker and dipivefrin hydrochloride, as well as with methazolamide. The remaining three eyes have no optic nerve damage or visual field loss and are not being treated with glaucoma medications as of the last follow-up visit.

Macular disease was the other important cause of early and late visual acuity loss in these eyes. Cystoid macular edema was present in nine eyes at the time of cataract extraction (Table 3). Cystoid macular edema that was not observed preoperatively or intraoperatively developed in one eye postoperatively, which resulted in a visual acuity of 20/40 (Table 3, Case 3, right eye). Preexisting cystoid macular edema resolved in three of nine eyes postoperatively; all three of these eyes achieved a visual acuity of 20/40 or better (Table 3, Case 1, left eye; Case 2, right eye; and Case 6, left eye). After resolution of observed cystoid macular edema, atrophic macular changes, presumably resulting from the prolonged cystoid macular edema, limited the visual acuity to 20/80 to 20/200 in another three of these nine eyes (Table 3, Case 4, right eye; and Case 10, both eyes). One of these patients (Table 3, Case 4, right eye) had an epiretinal membrane removed at the time of the posterior vitrectomy. The reduced postoperative visual acuity was in part related to the distortion of the macula caused by recurrence of this epiretinal membrane. On fluorescein angiography, these atrophic changes in the macula manifested as zones of transmission of the background choroidal fluorescence in areas of atrophic retinal pigment epithelium. Late fluorescein staining suggestive of cystoid macular edema was minimal in these eyes. Definite chronic cystoid macular edema persisted after cataract extraction in three of the nine eyes, which resulted in visual acuities of 20/200, 20/70, and 20/200 (Table 3, Case 2, left eye; Case 3, left eye; and Case 9, right eye, respectively). One of these eyes with chronic cystoid macular edema developed a macular hole that resulted in a visual acuity of 20/200 (Table 3, Case 2, left eye). Treatment of cystoid macular edema consisted of topical and posterior subtenon's injections of corticosteroids. Systemic corticosteroids or immunosuppressants were not used.

In this series, another possible cause of limited visual acuity after lensectomy and vitrectomy was amblyopia. One 6-year-old patient had preoperative right exotropia since early childhood. The best postoperative visual acuity in this patient was 20/60 (Table 3, Case 4, right eye). This patient also developed a recurrent epiretinal membrane in the macula, which reduced the visual acuity to 20/200 at 87 months of follow-up.

Discussion

Management of juvenile rheumatoid arthritis–associated cataracts by using automated vitrectomy instrumentation has been described.[2,9-12] Kanski and Shun-Shin[14] described a series of patients with systemic uveitis syndromes in childhood. This 1984 report included the results of cataract extraction in 162 eyes of patients with systemic uveitis syndromes in childhood, 61 of whom had the cataract removed by aspiration or discission and 101 of whom underwent lensectomy with limited anterior vitrectomy. Of these postlensectomy eyes, the recorded visual acuities were hand motions or less in 15% of the eyes, 20/400 to counting fingers in 30% of the eyes, and 20/60 or better in 55% of the eyes. No specific information was given about the average duration of follow-up for the juvenile rheumatoid arthritis–associated cases. A recent study[12] by Kanski in 1992 on lensectomy for complicated cataracts in juvenile chronic iridocyclitis had a mean postoperative follow-up period of five years four months. The main causes of postoperative visual acuity of 20/200 or less were glaucoma, amblyopia, and phthisis bulbi. Kanski[12] did not comment on the status of the macula in these patients during the postoperative course or compare the results from a limbal approach (97 eyes) to results from a pars plana approach (90 eyes).

TABLE 3
MACULAR CHANGES IN PATIENTS WITH JUVENILE RHEUMATOID ARTHRITIS

PATIENT NO.	EYE	FINAL VISUAL ACUITY	PREOPERATIVE CYSTOID MACULAR EDEMA*	POSTOPERATIVE MACULAR DISEASE	FOLLOW-UP (MOS)
1	L.E.	20/30	Present	Atrophic macular changes from chronic macular edema	57
2	R.E.	20/30	Present	Atrophic macular changes from chronic macular edema	31
	L.E.	20/200	Present	Macular hole from chronic macular edema	30
3	R.E.	20/40	Absent	Chronic macular edema	51
	L.E.	20/70	Present	Chronic macular edema	45
4	R.E.	20/200	Present	Recurrent epiretinal membrane	87
5	R.E.	20/300	Absent	Normal macula	122
	L.E.	20/50	Absent	Normal macula	12
6	R.E.	20/25	Absent	Normal macula	57
	L.E.	20/25	Present	Resolved macular edema	54
7	R.E.	4/200	Absent	Macular folds and hypotony after Molteno implantation	70
	L.E.	20/50	Absent	Normal macula	65
8	L.E.	20/20	Absent	Normal macula	51
9	R.E.	20/200	Present	Chronic macular edema	15
10	R.E.	20/100	Present	Atrophic macular changes from chronic macular edema	19
	L.E.	20/80	Present	Atrophic macular changes from chronic macular edema	18.5

*Cystoid macular edema was identified either preoperatively or at the time of the posterior vitrectomy.

Diamond and Kaplan[10] described two patients with juvenile rheumatoid arthritis who underwent pars plana lensectomy and vitrectomy. The resulting visual acuity was 20/25 in one patient and 20/70 in the other patient. Length of follow-up in their overall series of uveitic cataracts ranged from six to 38 months, but was not specifically indicated for these two patients. Algvere and associates[15] described four eyes of patients with juvenile rheumatoid arthritis who underwent lensectomy and vitrectomy or pupillary membrane removal. Two patients were followed up for two months, one for six months, and one for one year postoperatively. The visual acuity remained unchanged in one patient, improved to 20/200 in two patients, and improved to 20/100 in the final patient.

The initial results of pars plana lensectomy and vitrectomy in ten eyes were reported by our group in 1988[9] (eight of ten eyes are included in this present series). Two eyes were excluded from that previous series because follow-up was unavailable later than nine months postoperatively. The length of follow-up in our previous report ranged from six to 62 months (average, 17 months). In the current series, eight additional cases were added and longer follow-up (mean, 51 months) is provided on eight of ten eyes from our previous series.

In the current series, the two major obstacles to good visual acuity on long-term follow-up were chronic glaucoma and macular disease (Tables 2 and 3). Persistent glaucoma, which was present before lensectomy and vitrectomy, resulted in marked loss in visual acuity in two eyes in this series despite glaucoma surgery. One of these eyes developed retinal folds through the macula from surgery-induced chronic hypotony as described by Gass.[16] These macular folds in young myopic patients with hypotony may persist and cause permanent loss of visual acuity. Because chronic glaucoma develops frequently in patients with juvenile rheumatoid arthritis,[1,8,12] it is not known whether the pars plana lensectomy and vitrectomy aggravated the preoperative glaucoma.

Persistent cystoid macular edema was present in five eyes postoperatively and only one of these eyes had a visual acuity better than 20/60 with long-term follow-up (Table 3). Atrophic macular changes often followed the resolution of established cystoid macular edema and may have accounted for decreased final visual acuities in four eyes. The postoperative visual acuities in these eyes with atrophic macular changes remained poor but relatively stable on long-term follow-up.

Amblyopia may be a factor in the decreased visual acuity in these patients, as these cataracts often begin to form at an early age.[12] Only one patient in this series had long-standing exotropia and presumed amblyopia as a cause of reduced visual acuity. This patient also had a recurrent epiretinal membrane in the macula (Tables 2 and 3, Case 4).

The pars plana lensectomy and vitrectomy approach used in these cases theoretically allows complete removal of residual peripheral lens remnants by using scleral depression with vitrectomy over the ciliary body region. The posterior vitrectomy allows removal of the formed vitreous, which usually contains suspended inflammatory cells. Theoretically, by removing both the lens and the vitreous, the eye is decompartmentalized to allow more rapid clearing of inflammation in the event of subsequent uveitic episodes. In the current series, we could not correlate the amount of inflammation preoperatively or postoperatively with the final visual outcome or with complications such as glaucoma or cystoid macular edema. Although other surgical approaches may be equally successful in visual improvement, the long-term follow-up of those procedures has been limited.

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Prediction of Visual Recovery After Scleral Buckling of Macula-off Retinal Detachments

Thomas R. Friberg, M.D., and Andrew W. Eller, M.D.

Patients with rhegmatogenous retinal detachments involving the fovea have visual loss that may not be recoverable despite anatomically successful surgery. Few guidelines exist to predict ultimate visual outcome with any certainty. We found that despite macular detachment, a device commonly used to predict visual acuity in cataractous eyes, the Potential Acuity Meter (Mentor O & O, Inc., Norwell, Massachusetts), provided acuity measurements even when Snellen visual acuity levels were poor or unmeasurable. In a study of 50 consecutive patients with clear media, we investigated a possible correlation between postoperative Snellen visual acuity with the preoperative Potential Acuity Meter results. We found that actual visual improvement correlated well with potential visual improvement as determined by Potential Acuity Meter measurements (R = .92). Preoperative assessment of patients with this device was a better predictor of final visual outcome than preoperative Snellen visual acuity, the extent of retinal detachment, or the duration of the retinal detachment by history.

Generally, patients with rhegmatogenous retinal detachments involving the fovea have a dramatic reduction of visual acuity in the affected eye. Prediction of visual outcome by clinical variables is typically imprecise. We used a device that is commonly used to screen cataractous eyes, the Potential Acuity Meter[1] (Mentor O & O, Inc., Norwell, Massachusetts), and compared Potential Acuity measurements to three other preoperative variables that could influence ultimate visual acuity. These variables included the duration of retinal detachment, the extent of macular involvement, and the preoperative Snellen visual acuity. This study was initiated after a patient with a rhegmatogenous retinal detachment involving the fovea was serendipitously found to have a Potential Acuity Meter measurement of 20/40 even though her visual acuity was only counting fingers at 3 feet.

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From the Pittsburgh Eye and Ear Institute and the Department of Ophthalmology, University of Pittsburgh, Pittsburgh, Pennsylvania.

Reprint requests to Thomas R. Friberg, M.D., Eye and Ear Institute, 203 Lothrop St., Pittsburgh, PA 15213.

Material and Methods

All patients referred to us with primary rhegmatogenous retinal detachments in eyes with no more than minimal nuclear sclerosis were candidates for study. A careful history was obtained to determine how many weeks central vision had been decreased. Snellen visual acuity was measured by an ophthalmic technician, who was unaware of the purpose of the study, with the patient's corrective lenses in place. Pinhole visual acuity was also measured. In a few cases, the pinhole visual acuity was better than the Snellen visual acuity, and an overrefraction using spheres was conducted to attempt to improve the visual acuity further. The best Snellen visual acuity, either by using a pinhole or spheres, was recorded for these eyes. A brief retinal examination was performed to confirm the presence of macular involvement. The macula was considered to be detached if there was at least one disk diameter of subretinal fluid surrounding the fovea. We excluded patients with foveal splitting, as they tend to have a much more favorable prognosis than those with true macular detachment.[2]

Ten minutes after the screening examination, the same masked technician measured visual function by using the Potential Acuity Meter. The light beam that contained the eye chart image was directed through the pupil onto the posterior pole, and the instrument dial was

adjusted until the patient could see the chart most clearly. The end point was defined as the smallest line that contained multiple letters that the patient could read without making more than one error.

The retina was carefully assessed to locate the retinal breaks and to document the extent of macular detachment. Retinal detachments were classified into the following categories: category 1, in which the distance from the edge of the detachment to the detached foveola equaled approximately 1 disk diameter; category 2, in which the distance from the edge of the detachment to the detached foveola equaled from 1 to 2 disk diameters; category 3, in which the distance from the edge of the detachment to the detached fovea exceeded two disk diameters, but the retina was not totally detached; and category 4, in which the retina was totally detached.

Patients underwent surgical procedures within 48 hours of examination. In each case, cryotherapy to the retinal break, solid silicone buckling, and subretinal fluid drainage were performed.

Eyes were examined on several occasions postoperatively. At six months, a final refraction was obtained and the best-corrected visual acuity was recorded. Visual acuity measurements were again obtained by a masked technician under the same conditions used to examine the patients preoperatively. Initial scleral buckling failed in three of 53 patients enrolled, and these patients were excluded from analysis. The age of the remaining 50 patients ranged from 27 to 87 years (median age, 65 years).

Snellen visual acuities and Potential Acuity Meter results were converted to LogMAR units as described by Ferris and associates[3] by taking the logarithm of the reciprocal of the visual acuity value (Table 1). Using this conversion, the visual acuity values were converted to a linear scale, in which 20/20 visual acuity has a LogMAR value of 0, 20/40 a value of 0.3, 20/80 a value of 0.6, and 20/200 a value of 1.0. Counting fingers visual acuity was converted to a Snellen equivalent by recording the counting fingers distance as the numerator with a denominator of 200 as advocated by Faye.[4] Patients with hand motions visual acuity only were assigned a LogMAR value of 3.0. One patient with bare perception of hand motions

TABLE 1
PATIENTS WITH RECORDABLE* POTENTIAL ACUITY METER RESULTS WHO WERE UNABLE TO READ SNELLEN EYE CHART LETTERS†

PATIENT NO.	MEASURED VISUAL ACUITY‡	VISUAL ACUITY CONVERTED TO LOGMAR VALUE§	POTENTIAL ACUITY METER RESULT	POTENTIAL ACUITY METER RESULT CONVERTED TO LOGMAR VALUE§
1	HM	3.0	20/100	0.69
2	HM	3.0	20/200	1.00
3	HM	3.0	20/200	1.00
4	CF at 1 foot (1/200)	2.3	20/80	0.60
5	CF at 2 feet (2/200)	2.0	20/50	0.40
6	CF at 2 feet (2/200)	2.0	20/60	0.48
7	CF at 2 feet (2/200)	2.0	20/70	0.54
8	CF at 2 feet (2/200)	2.0	20/200	1.00
9	CF at 3 feet (3/200)	1.82	20/40	0.30
10	CF at 4 feet (4/200)	1.70	20/200	1.00
11	CF at 5 feet (5/200)	1.60	20/100	0.69
12	CF at 6 feet (6/200)	1.53	20/80	0.60
13	CF at 8 feet (8/200)	1.40	20/50	0.40

*Potential Acuity Meter result at least 20/400.
†Snellen visual acuity worse than 20/400.
‡HM indicates hand motions; CF indicates counting fingers.
§LogMAR value = log (1/Snellen equivalent).

visual acuity was assigned a LogMAR value of 3.6.

These data were analyzed by several methods. A multiple regression analysis was performed to evaluate the correlation of the four preoperative variables taken together (preoperative Potential Acuity Meter measurement, duration of retinal detachment, preoperative Snellen visual acuity, and extent of retinal detachment) with the ultimate Snellen visual acuity for all 50 patients. Linear and second- and third-order regression analyses were also performed in an attempt to correlate the individual variables with final visual acuity. To perform these analyses, we assigned a Potential Acuity Meter result of 20/800 to the 17 patients who were unable to read any of the instrument's eye chart letters. We also performed the identical analyses excluding these 17 patients. Finally, we calculated the odds of an eye recovering a certain visual acuity level given a certain Potential Acuity Meter test result.[5]

We also calculated the potential or predicted visual improvement for the 33 patients with recordable Potential Acuity Meter results. This value equals the preoperative Snellen visual acuity in LogMAR units minus the preoperative Potential Acuity Meter measurement.[5] Hence, a patient with poor preoperative Snellen visual acuity who has a good Potential Acuity Meter result would have a large potential visual improvement value. Actual visual improvement was defined as the preoperative Snellen visual acuity minus the postoperative Snellen visual acuity in LogMAR units. Potential visual improvement was plotted against actual visual improvement and the best-fit line was determined by linear regression analysis.

Results

Potential visual improvement correlated well (R = .92) with actual visual improvement (Fig. 1).

With respect to extent of retinal detachment, patients with total retinal detachments (category 4) had significantly poorer visual results compared to category 1 and category 2 patients by analysis of variance (P = .05).

The duration of each macular detachment in weeks was plotted against the final Snellen visual acuity for all 50 patients (Fig. 2). There was no significant correlation or trend.

The preoperative Snellen visual acuity was plotted against the postoperative Snellen visual acuity for all eyes (Fig. 3). There was a significant correlation between the preoperative and postoperative Snellen visual acuities (R = .59); the best-fit line was drawn. The correlation of the Potential Acuity Meter result vs final visual acuity for all 50 patients was significant (R = .72) (Fig. 4).

When the 17 patients with no recordable Potential Acuity Meter results were excluded, there also was a significant correlation between Potential Acuity Meter measurements and postoperative Snellen visual acuity (R = .49) (Fig. 5). For these same 33 patients, there was no significant correlation between preoperative and postoperative Snellen visual acuity (Fig. 6).

Using linear, polynomial, and multiple re-

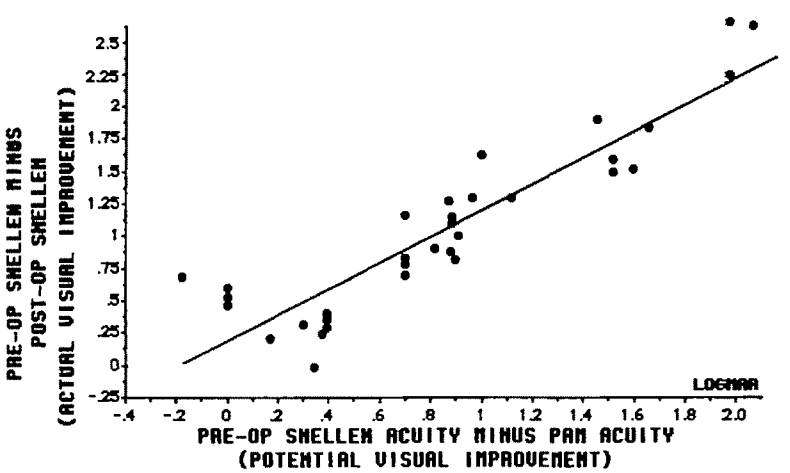


Fig. 1 (Friberg and Eller). A plot of actual visual improvement against potential visual improvement shows an excellent correlation between these calculated variables. Differences are in LogMAR units. By linear regression analysis, P = .0001 and R = .92. Pre-op indicates preoperative; post-op indicates postoperative; PAM indicates Potential Acuity Meter.

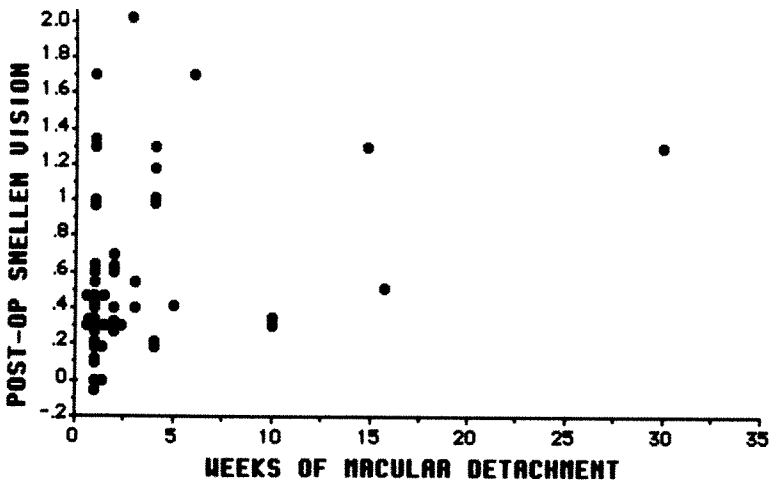


Fig. 2 (Friberg and Eller). The postoperative (post-op) Snellen visual acuity given in LogMAR units vs the duration of macular detachment as given by patient history (all patients) is plotted. There is no significant correlation between the two variables (P = .067).

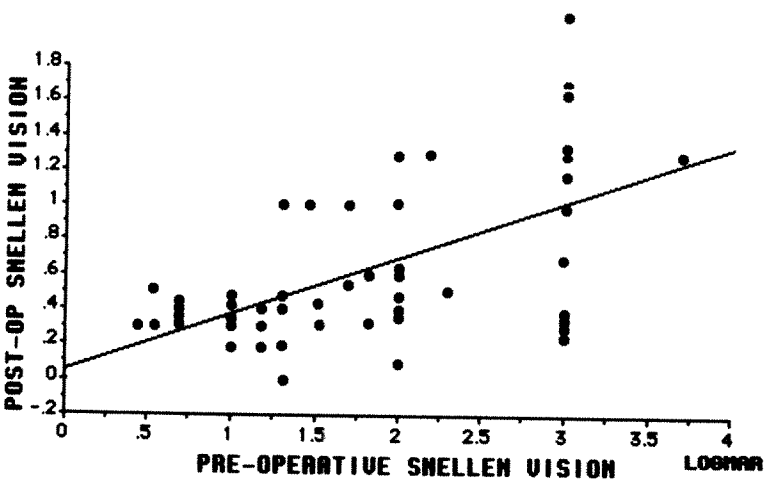


Fig. 3 (Friberg and Eller). The postoperative (post-op) Snellen visual acuity vs the preoperative Snellen visual acuity (both in LogMAR units) for all 50 patients is shown. By linear regression analysis, there is a significant correlation between these variables (P = .0001; R = .59).

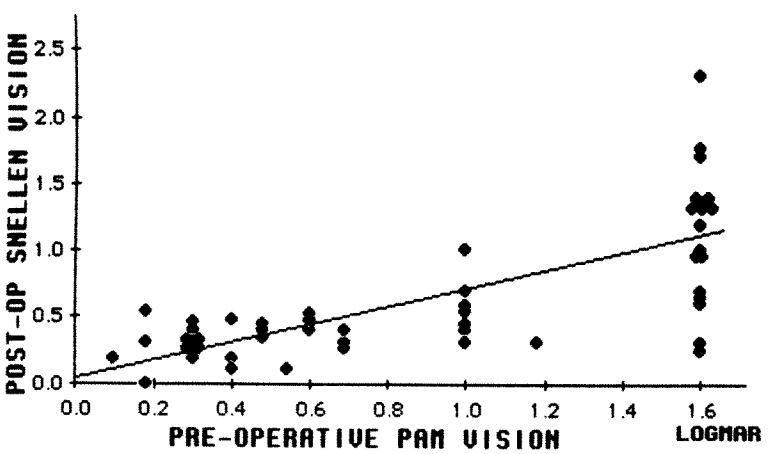


Fig. 4 (Friberg and Eller). The plot of postoperative (post-op) Snellen visual acuity vs Potential Acuity Meter (PAM) results for all 50 patients shows a significant correlation (P = .0001; R = .72).

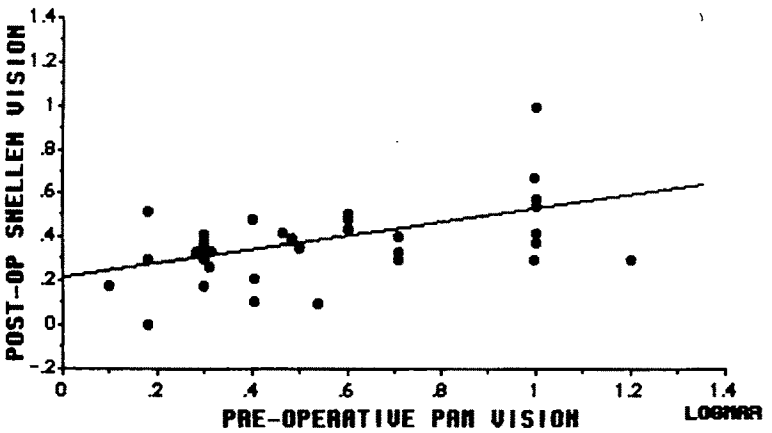


Fig. 5 (Friberg and Eller). In the 37 patients in whom a Potential Acuity Meter (PAM) measurement could be obtained, there was a significant correlation between postoperative (post-op) Snellen visual acuity and preoperative Potential Acuity Meter results (both in LogMAR units) by linear regression analysis (P = .004; R = .49).

gression analysis, the preoperative Potential Acuity Meter measurement was more highly correlated with the final visual acuity than any other variable (Tables 2 and 3).

Discussion

Preoperative visual acuity and the duration of foveal involvement have been used to help predict final visual acuity after successful retinal reattachment. Burton,[6] in a large series, determined preoperative visual acuities in patients with primary rhegmatogenous detachments repaired in one operation. Most had macular detachment. He found that 89% of patients who had 20/20 to 20/50 Snellen visual acuity maintained at least 20/50 visual acuity postoperatively. In contrast, fewer than 15% of patients with less than 20/200 preoperative visual acuity ultimately recovered a 20/50 value. Unfortunately, most patients with macula-off detachments have poor preoperative Snellen visual acuity, making it difficult to assess visual potential on the basis of this factor. In our series, 38 (78%) of the patients had a preoperative Snellen visual acuity worse than 20/200.

Other authors[6-8] described a similar relationship between preoperative and postoperative Snellen visual acuity in patients with macula-off retinal detachments. We also found that preoperative Snellen visual acuity was linearly correlated with ultimate visual outcome when all patients were considered (Fig. 3). Conversely, Potential Acuity Meter measurements were even more highly correlated with ultimate visual acuity (Figs. 3 through 6).

The prognostic relevance of the duration of

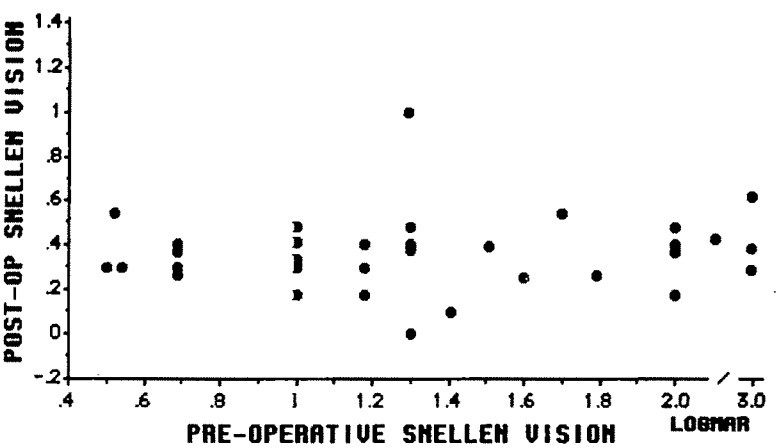


Fig. 6 (Friberg and Eller). When postoperative (post-op) Snellen visual acuity is plotted against preoperative Snellen visual acuity (both in LogMAR units) for the 37 patients in whom a definite Potential Acuity Meter (PAM) result could be obtained, there was no significant correlation (P = .40).

TABLE 2
COMPARISON OF PREOPERATIVE VARIABLES WITH FINAL VISUAL ACUITY

	LINEAR REGRESSION ANALYSIS y=F(x)				POLYNOMIAL REGRESSION y=F(x+x²)			
	ALL PATIENTS (N=50)		PATIENTS WITH OBTAINABLE POTENTIAL ACUITY METER RESULTS (N=33)		ALL PATIENTS (N=50)		PATIENTS WITH OBTAINABLE POTENTIAL ACUITY METER RESULTS (N=33)	
	R VALUE	PROBABILITY	R VALUE	PROBABILITY	R VALUE	PROBABILITY	R VALUE	PROBABILITY
Potential Acuity Meter result	.72	.0001	.49	.004	.74	.0001	.49	.017
Preoperative visual acuity	.59	.0001	.15	.40	.57	.0001	.19	.576
Detachment extent	.33	.02	.06	.73	.40	.016	.29	.271
Detachment duration	.26	.067	.10	.59	.26	.183	.11	.828

the macular detachment has been previously examined. Grupposo[7] found that while 75% of eyes with detachments of less than one week's duration achieved at least 20/70 postoperative visual acuity, macular involvement for one month reduced this figure to 59%. Tani, Robertson, and Langworthy[8] found a similar decrease in final visual acuity when the detachments were chronic. Burton,[6] by using nonlinear analysis, suggested that 71% of the variation in ultimate visual acuity could be attributed to the duration of macular involvement and emphasized the importance of prompt surgical repair. However, two thirds of his patients with retinal detachments were excluded from the analysis, as he considered their histories to be imprecise.

In our series, we found no significant linear or nonlinear correlation between the duration of macular detachment in weeks and the ultimate postoperative Snellen visual acuity (Fig. 2 and Table 2). In our experience, patients are often uncertain about when they noted visual impairment in the affected eye and their history may be inaccurate despite the physician's best efforts. Some patients become aware of their impairment only after the uninvolved eye is inadvertently occluded.[6] We believe a patient's reported duration of macular detachment is so imprecise compared to other variables that its prognostic value is limited.

When a rhegmatogenous detachment extends beyond the fovea, the fovea is frequently detached well away from the retinal pigment epithelium. This increased separation of the photoreceptors from the pigment epithelium might be expected to lead to a poorer visual prognosis because of a decreased transfer of nutrients and oxygen to the outer retina and possibly from

TABLE 3
MULTIPLE REGRESSION ANALYSIS OF PREOPERATIVE VARIABLES VS FINAL VISUAL ACUITY

	ALL PATIENTS* (N=50)		PATIENTS WITH OBTAINABLE POTENTIAL ACUITY METER RESULTS† (N=33)	
	COEFFICIENT	PROBABILITY	COEFFICIENT	PROBABILITY
Potential Acuity Meter result	.537	.0001	.336	.004
Preoperative visual acuity	.05	.537	−.021	.65
Detachment extent	.03	.554	−.003	.92
Detachment duration	.02	.151	.012	.20

*R=.75; P=.001.
†R=.534; P=.05.

TABLE 2 *(continued)*
COMPARISON OF PREOPERATIVE VARIABLES WITH FINAL VISUAL ACUITY

POLYNOMIAL REGRESSION $y=F(x+x^2+x^3)$			
ALL PATIENTS (N=50)		PATIENTS WITH OBTAINABLE POTENTIAL ACUITY METER RESULTS (N=33)	
R VALUE	PROBABILITY	R VALUE	PROBABILITY
.74	.0001	.52	.03
.60	.0001	.19	.77
.40	.04	.33	.33
.32	.16	.27	.53

the untoward effects of subretinal fluid. We found that eyes with total retinal detachments (category 4) had markedly poorer visual results than those with more limited macular involvement (categories 1 and 2). It is also likely that an eye with a complete detachment has had a more chronic macular separation, regardless of patient history.

In eyes with media opacities and no retinal detachment, Potential Acuity Meter as well as laser interferometer measurements have been shown to predict visual outcome reliably after successful cataract extraction or capsulotomy.[6,9,10] Additionally, Palestine and associates[11] showed that laser interferometry is valuable in determining which patients have a better visual prognosis before treatment for uveitis. In our series, using multiple regression analysis, the preoperative Potential Acuity Meter measurement was significantly correlated with ultimate visual outcome, whereas duration of macular detachment, preoperative visual acuity, and extent of detachment were less highly or not correlated with visual success (Table 3).

When the fovea is detached, the Potential Acuity Meter appears to provide a more sensitive method of measuring retinal function than Snellen visual acuity testing. No patient who could read at least one letter from the Snellen eye chart failed to read at least some of the instrument's letters. In contrast, 13 of the 50 patients could read no Snellen letters but could read letters by using the Potential Acuity Meter (Table 1).

The Potential Acuity Meter was particularly useful in predicting the degree of visual improvement for a given patient before successful scleral buckling. That is, if there was a large disparity between the Snellen visual acuity and Potential Acuity Meter measurement, there was a high likelihood that postoperatively the patient's visual acuity would improve by a similar amount (Fig. 1).

There are several reasons why the Potential Acuity Meter measurements might yield better prognostic information than Snellen visual acuity testing in patients with macula-off retinal detachments or those with cystoid macular edema.[9,12] The eye chart within the instrument, as projected through clear media, is much brighter than the Snellen visual acuity chart, perhaps by a log unit or more. More importantly, the tiny beam of light that contains the Potential Acuity Meter chart is not likely to scatter substantially as it passes through the retina toward the photoreceptors as the foveal region is illuminated almost exclusively during fixation. Conversely, when light reflected off a Snellen chart falls on a broad area of the cornea and illuminates the perifoveal retina as well as the fovea, intraretinal microcystic edema associated with the detachment probably produces considerable light scatter, which degrades the image as seen by the photoreceptors.

One might argue that careful refractions by using spheric and astigmatic lenses should have been performed on all our patients with macular detachments to optimize the Snellen visual acuity results. In our experience, the end points during such refractions are typically nebulous. We cannot, however, discount the possibility that the Potential Acuity Meter yields a better test of macular function because refractive errors have less of an influence on its test results than they do on Snellen visual acuity. Nevertheless, as a practical matter, Potential Acuity Meter testing takes only a minute or so to perform and is much more clinically expedient than determining refraction in an eye with a foveal detachment. It is necessary, however, to encourage patients with macula-off detachments to read as many letters as possible during both Potential Acuity Meter and Snellen visual acuity testing because the quality of the image they perceive is not optimal.

As a guideline for future patients with detachments, we developed odds ratios from our data to determine final visual results, assuming a given preoperative Potential Acuity Meter measurement.[6] If an individual's preoperative Potential Acuity Meter result was 20/80 or better, then that particular patient had a greater than 95% chance of visual recovery to the 20/60 or better level after a successful scleral

buckling procedure. By chance alone, a patient chosen at random from our population had a 58% likelihood of achieving 20/60 visual acuity. Conversely, any patient chosen from the same population had a 42% chance of having a worse than 20/60 visual acuity six months after scleral buckling. However, if that patient had a Potential Acuity Meter result worse than 20/80, then the likelihood of not recovering to the 20/60 Snellen level despite long-term anatomic reattachment would be 71%. Therefore, a good Potential Acuity Meter result is highly specific (95%) for predicting good visual recovery after a successful scleral buckling procedure, but the sensitivity is only moderately high (71%).

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OPHTHALMIC MINIATURE

And he was blind. At least from the standpoint of the natural-born body. But replacements had been made—at the prices which Eldritch could and would pay; that had been done just prior to his Prox voyage by Brazilian oculists. They had done a superb job. The replacements, fitted into the bone sockets, had no pupils, nor did any ball move by muscular action. Instead a panoramic vision was supplied by a wide-angle lens, a permanent horizontal slot running from edge to edge.

Philip K. Dick, *The Three Stigmata of Palmer Eldritch*
New York, Vintage Books, 1964, p. 162

Prevalence and Risk Factors of Diabetic Retinopathy Among Noninsulin-dependent Diabetic Subjects

Muh-Shy Chen, M.D., Chie-Shung Kao, M.D., Chih-Jen Chang, M.D., Ta-Jen Wu, M.D., Chen-Chung Fu, M.D., Chien-Jen Chen, Sc.D., and Tong-Yuan Tai, M.D.

In a population-based study in Taiwan, 11,478 subjects aged 40 years or older were screened for diabetes in one urban and five rural areas. Among the 715 subjects proven to have diabetes, 527 subjects underwent ophthalmoscopy. Diabetic retinopathy was present in 184 of the 527 subjects (35.0%), including background diabetic retinopathy in 157 subjects (30.0%), preproliferative diabetic retinopathy in 15 subjects (2.8%), and proliferative diabetic retinopathy in 12 subjects (2.2%). Diabetic retinopathy was correlated with the duration of diabetes and age at onset of diabetes, type of diabetes treatment, higher serum creatinine levels, and lower serum cholesterol levels. Several other factors, including gender, age, residential area, family income, educational level, control and family history of diabetes, body mass index, physical activity, exercise, cigarette smoking, stroke, ischemic heart disease, leg vessel disease, hypertension, and proteinuria, had no significant association with retinopathy. By multiple logistic regression analysis, duration of diabetes was the most important risk factor related to retinopathy. Diabetic subjects treated with insulin had a higher risk of developing retinopathy than those treated with dietary control (relative risk, 1.57; $.05 < P < .10$). The univariate analysis disclosed that proliferative diabetic retinopathy was related to older age at examination, older age at onset of diabetes, type of diabetes treatment, and presence of leg vessel disease. Insulin-treated diabetic subjects also had a higher risk of proliferative diabetic retinopathy than patients in whom diabetes was controlled by diet, with a relative risk of 2.51 ($.05 < P < .10$) in the multiple logistic regression analysis.

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From the Departments of Ophthalmology (Drs. M.-S. Chen and Kao), Public Health (Dr. C.-J. Chen), and Internal Medicine (Drs. Chang, Wu, Fu, and Tai), College of Medicine, National Taiwan University, Taipei, Taiwan, Republic of China. This study was supported by grant DOH75-0299-25 from the Department of Health, Executive Yuan, Taiwan, Republic of China (Dr. Tai).

Reprint requests to Tong-Yuan Tai, M.D., No. 7, Chung-Shan South Road, Department of Internal Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan, Republic of China.

In recent decades there has been an increase in the number of individuals with diabetes.[1] Noninsulin-dependent diabetic patients represent a large portion of such patients. With the economic development in Taiwan during the past few decades, the prevalence of diabetes mellitus among those aged 40 years or older has increased markedly. In the past three surveys performed in 1970, 1979, and 1986 in Taipei City, the prevalence of diabetes was 5.05%, 7.10%, and 8.17%, respectively.[2-5] In the rural areas of Taiwan, a prevalence of 5.06% was noted during a survey performed simultaneously with that of Taipei City in 1986. Diabetic retinopathy has now become a major cause of loss in visual acuity in adults, which is often insidious in noninsulin-dependent diabetes.[6]

Epidemiologic studies of diabetic retinopathy have been conducted among different populations in many areas of the world. The prevalence of diabetic retinopathy varies widely in different countries.[7-16]

Despite different study procedures and populations, several factors, including duration of diabetes,[7,8,11,14-32] age at the onset of diabetes,[7,11,16,17,21,25] age at examination,[15,18,19,21,22,26] type of diabetes treatment,[16,18,20,21] control of diabetes,[8,15,16,18,20-24,26,28-31,33-36] hypertension,[16,20,23,30,31,37,38] proteinuria,[11,16,20,21,23,30,36] serum creatinine level,[33] serum cholesterol level,[32,38] and body mass index,[13,16,21,23,31,38] have been found to correlate with the prevalence of diabetic retinopathy. In our population-based study, we investigated

the prevalence of diabetic retinopathy among noninsulin-dependent diabetic patients in Taiwan and determined the factors that correlated with the presence of retinopathy.

Subjects and Methods

This survey was conducted from November 1985 to June 1986. Among the 78 subdistricts of Ta-An Precinct in Taipei City, eight subdistricts were randomly selected. Five villages evenly distributed over the island (Suan-Shi, Bar-Ter, Zu-Tan, Su-Fu, and Chih-Ku villages) were also randomly selected.

The total number of subjects aged 40 years or older who underwent the diabetic survey in Taipei City was 4,272 (2,194 men and 2,078 women) and that of the five villages was 7,206 (3,582 men and 3,624 women), with a response rate of 65.3% and 72.0%, respectively.

With the help of specially trained public health nurses, all subjects were interviewed according to a structured questionnaire. The questionnaire included details on age, gender, height, weight, residential area, monthly family income, educational level, personal and family history of diabetes, degree of physical activity, frequency of exercise, and cigarette smoking.

The capillary blood glucose of each participant was examined either after an overnight fast or two hours postprandially. Diabetes mellitus was diagnosed according to the World Health Organization criteria.[39,40] Diagnosis was confirmed by a 75-g oral glucose tolerance test in those patients with equivocal diagnostic values.[40] By using these criteria, diabetes was diagnosed in 715 subjects, with a prevalence rate of 6.23%. Among the 715 subjects, 608 subjects, including 225 subjects in whom diabetes was newly diagnosed and 383 subjects in whom diabetes was previously diagnosed, participated in further systemic and laboratory examinations. Among the 383 patients in whom diabetes was previously diagnosed, 44 subjects were treated with insulin and 298 subjects were treated with sulfonylureas. Another 41 subjects treated by diet control only were checked for the blood glucose level criteria to confirm their diagnosis.

Diabetic control was classified as good, fair, or poor when the fasting plasma glucose levels of diabetic patients were 120 mg/dl or less, 121 to 140 mg/dl, and greater than 140 mg/dl, respectively; or when the two-hour postprandial levels were 160 mg/dl or less, 161 to 180 mg/dl, and greater than 180 mg/dl, respectively.[41] Venous blood was collected for serum creatinine, cholesterol, and high-density lipoprotein cholesterol measurements in all subjects. Proteinuria was determined by commercial urine strips.

According to the protocol of the World Health Organization Multinational Study on Vascular Disease in Diabetes,[42] large-vessel diseases, including stroke, ischemic heart disease, and leg vessel disease, were investigated. Stroke was defined when neurologic sequelae were present or when unilateral weakness lasted for more than 24 hours. Ischemic heart disease was diagnosed by history and electrocardiographic abnormalities as designated by the Minnesota Code.[42] Leg vessel disease was diagnosed by evidence of amputation or a history of intermittent claudication. Amputation was recorded when the subject had a history of gangrene and necrotic or surgical loss of tissue in the toe, foot, or leg because of arterial obstruction judged by the investigators and that occurred after the onset of diabetes.

Hypertension was deemed present when the systolic pressure was 160 mm Hg or greater, or when the diastolic pressure was 95 mm Hg or greater.[43]

Body mass index was measured by dividing the weight in kilograms by the square of height in meters. Those subjects with a body mass index of 25 to 30 kg of body weight/m^2 were deemed overweight and those with an index over 30 kg of body weight/m^2 were deemed obese. Physical activity was divided into light (sedentary), moderate, and heavy (laborious) groups. The exercise status (number of times per week) was classified as less than two, two to four, and five or more times per week. The duration of exercise was at least 30 minutes per day. The monthly family income and personal educational level were also investigated. The details of the geographic distribution of study areas and study methods have been described previously.[4,5]

Subjects who had not smoked more than 100 cigarettes in their lifetime were classified as nonsmokers; subjects who had smoked more than 100 cigarettes in their lifetime but had stopped smoking before the examination were classified as ex-smokers; and subjects who smoked at the time of the interview were classified as current smokers.

The ophthalmic examinations were performed with direct and indirect ophthalmoscopy after dilating the pupils with tropicamide

1% and phenylepinephrine 10%. The retinopathy status was divided into the following five categories: (1) no diabetic retinopathy; (2) background diabetic retinopathy, which was defined as the presence of one or more of the following clinical signs: microaneurysms, punctate or striate intraretinal hemorrhages, and hard exudates; (3) preproliferative diabetic retinopathy, which was defined as soft exudates, venous beading, and intraretinal microvascular abnormalities; (4) proliferative diabetic retinopathy, characterized by neovascularization on or within one disk diameter of the disk in extent, neovascularization elsewhere in the retina, and fibrous proliferative tissue; and (5) ungradable retinopathy, with media opacities, including leukoma from old trachoma and dense cataracts that precluded gradation of retinopathy. Diabetic subjects were classified according to the most severe changes in the worse eye. Ophthalmoscopy was performed in 527 of the diabetic subjects. All diabetic subjects had noninsulin-dependent diabetes, characterized by the absent symptoms of uncontrolled diabetes, including polyuria, polydipsia, and an evident weight loss at the time of diagnosis, and had not been treated with insulin during the first year after diagnosis.[4,6,40] The characteristics of 527 participants and 81 nonparticipants were similar. For participants and nonparticipants, the proportions of male gender were 45.0% and 46.9%, respectively; the mean ages ± standard deviation were 61.1 ± 9.3 years and 62.0 ± 8.9 years, respectively; the mean durations of diabetes ± standard deviation were 3.7 ± 5.3 and 3.9 ± 5.6 years, respectively; the percentages of subjects treated with insulin were 7.0% and 9.9%, respectively; the prevalences of hypertension were 31.7% and 35.8%, respectively; and the prevalences of proteinuria were 9.6% and 12.5%, respectively. For participants and nonparticipants, mean fasting plasma glucose levels ± standard deviation were 160.0 ± 66.9 mg/dl (375 subjects) and 171.5 ± 79.4 mg/dl (61 subjects), respectively, and mean two-hour postprandial levels ± standard deviation were 232.4 ± 79.0 mg/dl (186 subjects) and 212.4 ± 68.5 mg/dl (20 subjects), respectively. The differences in the previously mentioned characteristics were not significant. There were also no significant differences for residential area, income, educational level, age at onset of diabetes, body mass index, physical activity, exercise, cigarette smoking, large-vessel disease, and serum levels of creatinine, cholesterol, and high-density lipoprotein cholesterol.

The statistical significance was assessed by using the Student's *t*-test and the chi-square test. Correlation coefficients were estimated by Spearman's method and multiple logistic regression analysis was also performed to evaluate multivariate-adjusted associations between related factors and diabetic retinopathy.

Results

The retinopathy status of the 527 participating subjects (237 men and 290 women) was determined by age and gender (Table 1). Diabetic retinopathy was present in 184 of the 527 subjects (35.0%). Background diabetic retinopathy was present in 157 subjects (30.0%), preproliferative diabetic retinopathy was present in 15 subjects (2.8%), and proliferative diabetic retinopathy was present in 12 subjects (2.2%). No diabetic retinopathy was present in 334 subjects (63.3%) and retinopathy was ungradable in nine subjects (1.7%).

The relationship between the prevalence of retinopathy and sociodemographic characteristics was investigated. The difference in prevalence was not statistically significant between men and women. The prevalence of retinopathy was not statistically different when the subjects were divided according to age (40 to 49 years, 50 to 59 years, 60 to 69 years, and 70 years or older). However, the oldest diabetic subjects had the highest prevalence of proliferative diabetic retinopathy ($P < .05$ on the basis of a chi-square test). Residential area, monthly family income, and educational level were not significantly associated with retinopathy.

Family history of diabetes, body mass index, degree of physical activity, frequency of exercise, and cigarette smoking were not associated with the prevalence of either total retinopathy or proliferative diabetic retinopathy.

Subjects with a longer duration of diabetes had a higher percentage of total retinopathy (Table 2) ($P < .01$ on the basis of a chi-square test).

The prevalence of retinopathy was different among subjects with different types of diabetic treatment ($P < .01$). The subjects treated with insulin had a higher prevalence of total retinopathy (58.3%) and proliferative diabetic retinopathy (8.3%) than subjects not treated with insulin (35.8% and 1.9%, respectively) (Table 2).

The control of diabetes and the prevalence of total and proliferative diabetic retinopathy were not associated (Table 2). However, for all categories of retinopathy, those subjects with

TABLE 1
PREVALENCE OF RETINOPATHY STATUS BY AGE AT EXAMINATION AND GENDER IN DIABETIC SUBJECTS

AGE AT EXAMINATION (YRS)	GENDER	RETINOPATHY STATUS OF SUBJECTS: NO DIABETIC RETINOPATHY NO.	(%)	BACKGROUND DIABETIC RETINOPATHY NO.	(%)	PREPROLIFERATIVE DIABETIC RETINOPATHY NO.	(%)	PROLIFERATIVE DIABETIC RETINOPATHY NO.	(%)	UNGRADABLE RETINOPATHY NO.	(%)
40–49	M	9	(50.0)	9	(50.0)	0	—	0	—	0	—
	F	30	(73.2)	11	(26.8)	0	—	0	—	0	—
50–59	M	44	(62.9)	21	(30.0)	4	(5.7)	1	(1.4)	0	—
	F	70	(67.3)	29	(27.9)	4	(3.8)	1	(1.0)	0	—
60–69	M	66	(61.7)	36	(33.6)	2	(1.9)	1	(0.9)	2	(1.9)
	F	54	(61.4)	27	(30.7)	3	(3.4)	3	(3.4)	1	(1.1)
70 years or older	M	28	(66.7)	10	(23.8)	1	(2.4)	1	(2.4)	2	(4.8)
	F	33	(57.9)	14	(24.6)	1	(1.8)	5	(8.8)	4	(7.0)
Total											
	M	147	(62.0)	76	(32.1)	7	(2.9)	3	(1.3)	4	(1.7)
	F	187	(64.5)	81	(27.9)	8	(2.8)	9	(3.1)	5	(1.7)

poor control of diabetes seemed to have a higher prevalence as compared with those subjects with good control of diabetes.

The association of prevalence of total retinopathy with large-vessel diseases, including stroke, ischemic heart disease, and leg vessel disease, was not statistically significant. However, the subjects with leg vessel disease had a higher prevalence of proliferative diabetic retinopathy than the subjects without leg vessel disease (22.2% and 2.0%, respectively; $P < .05$). The prevalence of total retinopathy

TABLE 2
PREVALENCE OF VARIOUS RETINOPATHY BY DURATION, TREATMENT, AND CONTROL STATUS OF DIABETES

VARIABLES	RETINOPATHY STATUS OF SUBJECTS: BACKGROUND DIABETIC RETINOPATHY NO.	(%)	PREPROLIFERATIVE DIABETIC RETINOPATHY NO.	(%)	PROLIFERATIVE DIABETIC RETINOPATHY NO.	(%)	TOTAL NO.	(%)
Duration of diabetes (yrs)								
Newly diagnosed (N=187)	41	(21.9)	1	(0.5)	1	(0.5)	43	(23.0)*
< 4 (N=187)	57	(30.5)	3	(1.6)	6	(3.2)	66	(35.3)
5–9 (N=75)	28	(37.3)	6	(8.0)	3	(4.0)	37	(49.3)
> 10 (N=69)	31	(44.9)	5	(7.3)	2	(2.9)	38	(55.1)
Type of diabetes treatment								
Diet control (N=164)	42	(25.6)	2	(1.2)	3	(1.8)	47	(28.7)*
Oral hypoglycemic agent (N=318)	101	(31.8)	9	(2.8)	6	(1.9)	116	(36.5)
Insulin (N=36)	14	(38.9)	4	(11.1)	3	(8.3)	21	(58.3)
Control of diabetes†								
Good (N=124)	36	(29.0)	1	(0.8)	3	(2.4)	40	(32.3)
Fair (N=72)	20	(27.8)	1	(1.4)	0	—	21	(29.2)
Poor (N=322)	101	(31.4)	13	(4.0)	9	(2.8)	123	(38.2)

*$P < .01$, chi-square test.

†Good, fair, or poor control defined as follows: fasting plasma glucose levels were ≤ 120 mg/dl, 121 to 140 mg/dl, and > 140 mg/dl, respectively; or two-hour postprandial levels were ≤ 160 mg/dl, 161 to 180 mg/dl, and > 180 mg/dl, respectively.

seemed to be higher in the subjects with hypertension (37.0%) and proteinuria (45.5%) than in the subjects without hypertension and proteinuria (33.0% and 34.6%, respectively), though the difference was not statistically significant.

The subjects with retinopathy had a higher level of serum creatinine than those without retinopathy (mean ± standard deviation, 1.08 ± 0.40 mg/dl and 1.06 ± 0.34 mg/dl, respectively; $P < .05$). However, the subjects with retinopathy had a lower level of serum cholesterol than those without retinopathy (mean ± standard deviation, 199.6 ± 41.2 mg/dl and 191.0 ± 44.6 mg/dl, respectively; $P < .05$). The serum high-density lipoprotein cholesterol level was not associated with the prevalence of retinopathy.

The duration of diabetes was the only factor significantly associated with retinopathy as analyzed by a multiple logistic regression model. For every one-year increment in the duration of diabetes, the risk of retinopathy increased 1.07 times ($P < .005$). In other words, for a ten-year increase in diabetes duration, the relative risk of developing retinopathy was as high as 1.95. The insulin-treated diabetic subjects had a higher risk of developing retinopathy than those subjects treated with dietary control (relative risk, 1.57; $.05 < P < .10$) (Table 3). Regarding proliferative diabetic retinopathy, insulin-treated diabetic subjects also had a higher risk than subjects with diabetes controlled by diet (relative risk, 2.51; $.05 < P < .10$) (Table 4).

Discussion

Studies from Australia,[7,8] Denmark,[9,10] Iceland,[11] Sweden,[12,13] and the United States[14-16] showed a large difference in prevalence, which ranged from 24% to 70% for total diabetic retinopathy and from 4.5% to 22% for proliferative diabetic retinopathy. Our study showed a prevalence of 35.0% for diabetic retinopathy and 2.2% for proliferative diabetic retinopathy in noninsulin-dependent diabetic subjects. The prevalence of proliferative diabetic retinopathy in our study was compared to the data from the Western studies. One study[8] found prevalences of total diabetic retinopathy and proliferative diabetic retinopathy to be 24% and 4.5%, respectively, among adults; one study[10] found prevalences of 40.9% and 3.3%, respectively, among subjects treated with oral hypoglycemic agents; and one study[16] found prevalences of 62.0% and 10.0%, respectively, among subjects older than 30 years. In comparison, the prevalence of proliferative diabetic retinopathy among Chinese adult patients with noninsulin-dependent diabetes was low, although the total prevalence of 35% was not remarkably different.

The duration of diabetes and the prevalence and severity of retinopathy were closely associated (Table 2). The longer the duration of diabetes, the higher the prevalence of total retinopathy. The prevalences of total and proliferative diabetic retinopathy were 29.1% and 1.9%,

TABLE 3
MULTIPLE LOGISTIC REGRESSION ANALYSIS OF FACTORS ASSOCIATED WITH PREVALENCE OF RETINOPATHY

FACTORS	COMPARISON	PREVALENCE ODDS RATIO	95% CONFIDENCE INTERVAL	P VALUE*
Duration of diabetes	Every 1-yr increment	1.07	1.02–1.12	< .005
Age at onset	Every 1-yr increment	1.00	0.98–1.03	N.S.
Type of diabetes treatment	Diet vs oral hypoglycemic agent	0.81	0.60–1.10	N.S.
	Diet vs insulin	1.57	0.95–2.59	.05 < P < .1
Control of diabetes	Fair vs good	0.84	0.57–1.23	N.S.
	Poor vs good	1.15	0.87–1.53	N.S.
Serum creatinine	Every 1-mg/dl increment	1.36	0.82–2.27	N.S.
Serum cholesterol	Every 1-mg/dl decrement	1.00	0.99–1.00	N.S.

*N.S. indicates not significant.

TABLE 4
MULTIPLE LOGISTIC REGRESSION ANALYSIS OF FACTORS ASSOCIATED WITH PREVALENCE OF PROLIFERATIVE DIABETIC RETINOPATHY

FACTORS	COMPARISON	PREVALENCE ODDS RATIO	95% CONFIDENCE INTERVAL	P VALUE*
Age at examination	Every 1-yr increment	1.10	0.98–1.25	N.S.
Age at onset	Every 1-yr increment	0.99	0.89–1.10	N.S.
Type of diabetes treatment	Diet vs oral hypoglycemic agent	0.72	0.33–1.55	N.S.
	Diet vs insulin	2.51	0.90–6.99	$.05 < P < .1$
Control of diabetes	Fair vs good	0.56	0.13–2.40	N.S.
	Poor vs good	1.22	0.49–3.02	N.S.
Leg vessel disease	Yes vs no	1.48	0.83–2.65	N.S.

*N.S. Indicates not significant.

respectively, for those subjects who had diabetes for less than five years, and 23.0% and 0.5%, respectively, for subjects in whom diabetes was newly diagnosed. These data emphasized that the onset of noninsulin-dependent diabetes was difficult to determine precisely, and apparently diagnosis was delayed in many patients. Similar results have also been emphasized in other studies.[16,44] Some studies found that the duration of diabetes is the most crucial factor for both total and proliferative diabetic retinopathy.[23,25] However, our results showed that duration of diabetes was related to the prevalence of total retinopathy, but not to proliferative diabetic retinopathy. The difficulty in determining the exact duration of diabetes and the small number of subjects with proliferative diabetic retinopathy explain at least in part the nonsignificant association between duration of diabetes and proliferative diabetic retinopathy.

Similar to[16,18,20,21] or in contrast to[44] the results of other studies, our univariate analysis showed a higher prevalence of total and proliferative diabetic retinopathy in insulin-treated diabetic subjects. In Taiwan, it was difficult to persuade noninsulin-dependent diabetic patients who resisted treatment with oral hypoglycemic agents to consent to treatment with insulin. The subjects who were treated with insulin injection were reluctant to accept treatment with two or more doses a day. Thus, those subjects treated with insulin usually had a longer duration and poorer control of diabetes.[45]

Whether good diabetic control reduces the development of diabetic retinopathy is still controversial. Our cross-sectional study showed no statistically significant relationship between diabetic control and prevalence of retinopathy, although our results did demonstrate that subjects with good control of diabetes seemed to have a lower prevalence of total retinopathy (32.2%) than those with poor control of diabetes (38.2%).

The renal dysfunction, as indicated by increased creatinine levels and proteinuria, has been shown to be associated with retinopathy.[16,20,23,25] Both factors are assumed to signify generalized microvascular disease in individuals with diabetes. Our data demonstrated that the prevalence of total retinopathy was correlated with increased creatinine levels and was higher in diabetic subjects with proteinuria. But the associations were not statistically significant after adjusting for duration of diabetes. Recently, more sensitive tests for measuring microalbuminuria showed a correlation to the development of retinopathy.[46]

No association[30] or weak association[31] between serum cholesterol level and retinopathy was described, although few studies found positive association.[32,38] The association between serum cholesterol level and retinopathy was not statistically significant with a multivariate-adjusted odds ratio of 1.0 in our investigation. There was no correlation between retinopathy and large-vessel diseases. However, the higher prevalence of proliferative diabetic retinopathy in subjects with leg vessel disease deserves further evaluation.

In our series, proliferative diabetic retinopathy was present in only 12 subjects. The preva-

lence odds ratios for age at examination, control of diabetes, and leg vessel disease were 1.10, 1.22, and 1.48, respectively. The associations were not statistically significant; however, they might become significant if the sample size increased.

Ophthalmoscopy is not as good as fundus photography for the detection of diabetic retinopathy. Fundus photography can offer permanent records of retinopathy and accurately document subtle changes in retinopathy over time.[47,48] Because fundus photography could not be performed in all subjects at the time of our large field study, the use of ophthalmoscopy might have affected the estimated prevalence of diabetic retinopathy to some extent. Because ophthalmoscopy was performed by well-experienced ophthalmologists who did not know the risk factors of diabetic retinopathy, the prevalence odds ratios observed between risk factors and retinopathy were considered conservative estimates.

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Cytokines in the Vitreous of Patients With Proliferative Diabetic Retinopathy

Ahmed M. Abu El Asrar, M.D., Davide Maimone, M.D., Peter H. Morse, M.D., Susan Gregory, Ph.D., and Anthony T. Reder, M.D.

Sixteen vitreous and paired serum samples from 13 patients with proliferative diabetic retinopathy, vitreous samples from seven cadaveric control subjects, and aqueous humor samples from 15 normal control subjects were assayed for the cytokines interleukin-1, tumor necrosis factor-α, interleukin-6, and interferon-γ. Interleukin-6 was detected in 15 of 16 vitreous samples (94%) from diabetic patients, but it was not detected in any of the aqueous humor samples. Vitreous interleukin-6 levels positively correlated with ocular disease activity. Interleukin-1 was detected in seven of 16 vitreous samples (44%) and in four of ten aqueous humor samples (40%), whereas tumor necrosis factor-α and interferon-γ were never detected in vitreous or aqueous fluid. Serum samples from diabetic patients and control subjects contained comparable low levels of interleukin-6. Interleukin-1, tumor necrosis factor-α, and interferon-γ were not found in any of the sera. Because interleukin-6 can function as B-cell differentiation factor, this cytokine may have a role in immunoglobulin deposition in the ocular tissues and in the immunopathologic characteristics of proliferative retinopathy.

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From the Department of Ophthalmology, Mansoura University Hospital, Mansoura, Egypt (Dr. Abu El Asrar); and the Departments of Neurology and Brain Research Institute (Drs. Maimone and Reder), Ophthalmology and the Visual Sciences Center (Dr. Morse), and Medicine (Dr. Gregory), The University of Chicago, Chicago, Illinois. This study was supported in part by the Peace Fellowship Programme for Egypt, sponsored by the Agency for International Development, Washington, DC; a Harry Weaver Neuroscience Award from the National Multiple Sclerosis Society, New York, New York; and grant 1 K08 NS 01068-01 from the National Institutes of Health-Public Health Service (Dr. Reder).

Reprint requests to Peter H. Morse, M.D., Visual Sciences Center, 939 E. 57th St., Chicago, IL 60637-1454.

THE PATHOGENESIS of proliferative retinopathy is incompletely understood, but immunologic mechanisms may have a role in the development of the characteristic microangiopathy.[1] Ocular deposits of immunoglobulin and complement have been detected in patients with diabetic retinopathy.[2-4] The preretinal membranes in individuals with diabetes contain activated B lymphocytes, T cells, and monocytes, and class II major histocompatibility complex antigen expression is found at the level of the pigmented epithelium.[3,4] Additionally, it is our clinical impression that some eyes with proliferative diabetic retinopathy, especially in type I diabetics, show clinical signs of inflammation such as injected, irritated eyes, and cells and flare in the anterior chamber.

Cytokines are polypeptides produced by immune cells that regulate immune responses and inflammatory reactions. Some cytokines could trigger or maintain proliferative retinopathy. Among relevant cytokines, interleukin-1β and tumor necrosis factor-α have angiogenic activity,[5,6] stimulate glial cell proliferation,[7,8] and induce fibroblast proliferation and collagen synthesis.[9] Interleukin-6 induces the final differentiation of B cells to antibody-producing cells.[10] Interferon-γ is a potent inducer of class II major histocompatibility complex antigens.[11-13] Several studies in mice suggest that the dysregulation of cytokine production or the production of abnormal cytokines could be responsible for the hyperactivation of autoantibody-producing B cells.[14,15] Intraocular secretion of cytokines could explain ocular deposits of immunoglobulin in patients with proliferative diabetic retinopathy.

To explore immunologic mechanisms in the pathogenesis of proliferative retinopathy, we examined the vitreous and serum from patients with proliferative diabetic retinopathy for the presence of interleukin-1β, tumor necrosis factor-α, interleukin-6, and interferon-γ.

Subjects and Methods

Subjects—Vitreous and paired serum samples were obtained from 13 patients with proliferative diabetic retinopathy who underwent vitrectomy for nonclearing vitreous hemorrhage (13 eyes) or traction macular detachment (three eyes). In three patients, a second vitreous and serum sample was obtained intraoperatively on the fellow eye. The patients included eight men and five women whose ages ranged from 24 to 88 years, with an average of 51 years. The patients had a duration of diabetes from nine to 30 years, with an average of 20 years, and all were insulin dependent.

The preoperative and operative findings were recorded and the clinical disease severity was graded from 0 to 4 according to the presence and extent of active fibrovascular tissue, vitreous hemorrhage, iris neovascularization (rubeosis iridis), and hyphema. Grade 0 denoted inactive residual fibrous tissue from proliferative diabetic retinopathy; grade 1+ denoted vitreous hemorrhage without active neovascularization; grade 2+ denoted vitreous hemorrhage with actively growing fibrovascular tissue; grade 3+ denoted iris neovascularization in addition to the findings in grade 2+; and grade 4+ denoted hyphema in addition to the findings in grade 3+.

Two patients had renal transplants and were taking immunosuppressive drugs. The first patient was being treated with prednisone, cyclosporine, and azathioprine (1+ disease activity; the interleukin-6 level was 1.84 pg/ml). The second patient was being treated with prednisone and cyclosporine (3+ disease activity; the interleukin-6 level was 15 pg/ml).

Vitreous samples were also obtained after death in seven patients with no history of intraocular disease, ocular trauma, or sepsis. Vitreous was harvested four to seven hours post mortem. One additional control donor underwent a vitrectomy during repair of a macular hole.

Aqueous samples from 15 nondiabetic subjects who had no history of ocular inflammation were obtained at the time of cataract extraction. These samples were used as a control for the normal intraocular cytokine levels. The aqueous fluid was used as a control sample because removal of vitreous from normal eyes is contraindicated. Furthermore, there is communication and exchange between the fluid content in the anterior chamber and the posterior segment of the eye, especially in elderly patients with liquified vitreous. In preliminary experiments, interleukin-6 was found at marked levels in the vitreous of seven nondiabetic cadaveric eyes within three to eight hours of death. Because of the variability of fresh donor vitreous, aqueous was used as a control.

The samples were centrifuged, and the supernatants were frozen at −70 C until they were assayed.

Interleukin-6 bioassay—An interleukin-6–dependent mouse hybridoma cell line, B9, was used (L. A. Aarden, M.D., Central Laboratory of Netherlands Red Cross Blood Transfusion Service, University of Amsterdam, The Netherlands).[16] After one wash, cells were resuspended in Iscove's modified Dulbecco's medium supplemented with 5% fetal bovine serum, 5×10^{-5} mol/l mercaptoethanol, penicillin, and streptomycin, and seeded in 96-well flat-bottomed microwell plates at a density of 5,000 cells/200 μl/well. Vitreous samples were assayed without further treatment. All sera were heat-inactivated at 56 C for 30 minutes to prevent a nonspecific toxic effect to the B9 cells. Serial dilutions of each sample were added in triplicate to the wells. Proliferation was evaluated after 72 hours by measuring the amount of radioactivity incorporated after a four-hour pulse with 1 μCi of [^{3}H] thymidine. Sample values were always compared to a standard curve generated with recombinant human interleukin-6 (S. Gillis, M.D., Immunex, Inc., Seattle, Washington) or natural human interleukin-6 (Endogen, Inc., Boston, Massachusetts). No inhibitory activity on B9-cell proliferation was observed in the vitreous or serum after the addition of various amounts of recombinant human interleukin-6. The detection limit in vitreous and serum was 1.0 pg/ml.

Neutralization with anti-interleukin-6 antiserum—To assess the specificity of the interleukin-6 activity in our vitreous samples, we performed neutralization tests with a commercially available rabbit antiserum specific for human interleukin-6 (Endogen, Inc.). Aliquots of vitreous were incubated at 37 C for three hours with various concentrations of rabbit anti-interleukin-6 or equivalent doses of preimmmune rabbit serum (Endogen, Inc.). Duplicate aliquots (100 μl each) of neutralized specimens were assayed for their ability to induce proliferation of the B9 cells as described.

Tumor necrosis factor-α enzyme-linked immunosorbent assay (ELISA)—Tumor necrosis factor-α measurements were performed with an

ELISA kit (Cistron Biotechnology, Pine Brook, New Jersey). Undiluted vitreous and sera were tested in duplicate by adding 100 μl/well. A standard curve was run in each assay with predetermined amounts of recombinant human tumor necrosis factor-α (range, 20 to 1,000 pg/ml). This method showed a detection limit of 20 pg/ml of tumor necrosis factor-α. The standard curve was not altered by dilution of recombinant human tumor necrosis factor-α in pooled normal human sera.

Interleukin-1β ELISA—Interleukin-1β was quantitated with an ELISA kit (Cistron Biotechnology). The assay was used according to the manufacturer's instructions. Duplicate aliquots of 100 μl of undiluted vitreous and serum were tested. The standard curve obtained with recombinant human interleukin-1β ranged from 20 to 1,000 pg/ml. The detection limit was 20 pg/ml. The standard curve was not altered by dilution of recombinant interleukin-1β in pooled normal human sera.

Interferon-γ ELISA—Interferon-γ was quantitated with an ELISA kit (Amgen Biological, Thousand Oaks, California). The assay was used according to the manufacturer's instructions. Duplicate aliquots of 100 μl of undiluted vitreous and serum were tested. The detection limit was 6.25 U/ml. The standard curve ranged from 6.25 to 50 U/ml.

Statistical analysis—Data were analyzed by using one-tailed paired or unpaired *t*-tests, Mann-Whitney U tests, and linear regression analysis as appropriate. A P value less than .05 was considered significant. Values were expressed as mean ± standard error of the mean.

Results

Cytokines in ocular fluids—Interleukin-6 was detected in 15 of 16 vitreous samples (94%) from patients with proliferative diabetic retinopathy. The levels of detectable interleukin-6 in the vitreous samples ranged from 1.14 to 190 pg/ml ± (43.3 ± 15.7 pg/ml; mean ± standard error of the mean) (Fig. 1). Interleukin-6 was not detected in any of the aqueous samples from 15 normal control subjects (vitreous samples vs aqueous samples, $P < .005$; Mann-Whitney U test).

In vitreous fluid from control subjects (seven post mortem), interleukin-6 levels ranged from 0 to 49.5 pg/ml (9.80 ± 6.05 pg/ml). Interleukin-6 values in these control subjects were lower than in patients with proliferative diabetic retinopathy ($P < .03$, unpaired *t*-test).

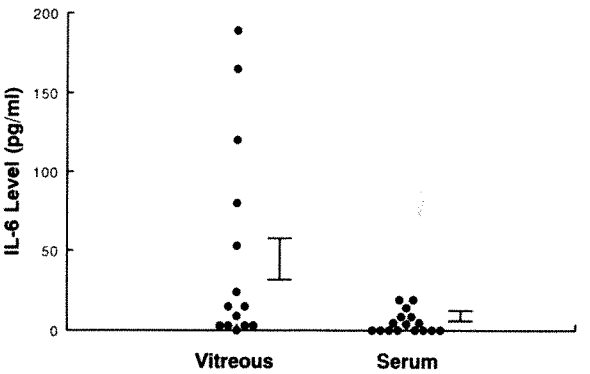


Fig. 1 (Abu El Asrar and associates). Detectable interleukin-6 (IL-6) levels in vitreous and paired serum samples from 16 eyes. One vitreous sample and eight serum samples had interleukin-6 levels less than 1 pg/ml.

Interleukin-6 levels in the vitreous samples of patients with proliferative diabetic retinopathy were positively correlated with the grade of clinical ocular disease severity (Fig. 2) ($R = 0.677$, $P < .004$; linear regression analysis). The two diabetic patients with renal transplants had interleukin-6 levels of 1.84 pg/ml (disease activity, 1+) and 15 pg/ml (disease activity, 3+).

The presence of specific interleukin-6 activity in vitreous samples was confirmed by using a rabbit anti-human interleukin-6 in neutralization tests. The proliferative response of B9 cells to interleukin-6 from vitreous samples was completely blocked by the rabbit antiserum.

Interleukin-1β protein was detected in seven of 16 vitreous samples (44%), with levels ranging from 21 to 68 pg/ml. Interleukin-1β was present in four of ten aqueous samples, with levels ranging from 36 to 59 pg/ml.

Tumor necrosis factor-α and interferon-γ were not detected in any of the vitreous samples from patients with proliferative diabetic retinopathy or aqueous samples from control subjects.

Cytokines in the serum—Interleukin-6 was detected in eight of the 16 serum samples (50%). The serum interleukin-6 level ranged from 1.1 to 21.4 pg/ml (Fig. 1). These levels were not different from those found in the serum of normal control samples assayed in our laboratory. Interleukin-6 levels in the vitreous samples were higher than those in paired sera ($P < .05$; paired *t*-test).

Interleukin-1β, tumor necrosis factor-α, and

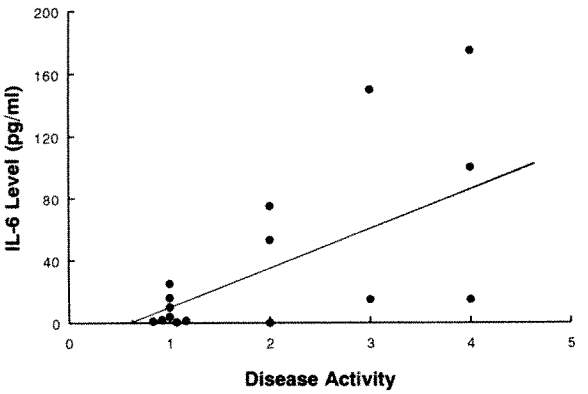


Fig. 2 (Abu El Asrar and associates). Correlation of interleukin-6 (IL-6) levels in vitreous samples with clinical disease activity in 16 eyes from patients with proliferative diabetic retinopathy.

interferon-γ were not detected in any of the sera.

Discussion

In our study, interleukin-6 was found in 15 of 16 vitreous samples (94%) from patients with proliferative diabetic retinopathy. Interleukin-6 was not present in aqueous samples from normal control subjects and was also significantly lower in postmortem vitreous samples from subjects without intraocular disease. In postmortem eyes, the delay between death and harvesting of vitreous would be expected to increase vitreous protein,[17] including interleukin-6, which implies that the interleukin-6 found in fresh vitreous in proliferative diabetic retinopathy is biologically important. It is possible that compartments such as the vitreous act as a reservoir for cytokines, thus amplifying local effects.

The levels of interleukin-6 correlate with clinical disease severity in eyes as graded by our criteria (Fig. 2). An increase of interleukin-6 was not detected in paired serum samples, suggesting that interleukin-6 in the vitreous is intraocular in origin and designates proliferative retinopathy. The inference that interleukin-6 synthesis is local would theoretically be confirmed by Northern blot analysis of retinal tissue, but retinal or iris biopsy is not performed in patients undergoing vitrectomy for proliferative diabetic retinopathy.

Interleukin-6 can be produced by various cell types, including monocytes, activated T cells,[18] vascular endothelial cells, fibroblasts,[19] and glial cells.[20] These cells could be the source of intraocular interleukin-6 in patients with proliferative retinopathy caused by diabetes and possibly by sickle cell disease, retinal detachment, and retinal vein occlusion.

Interleukin-6, also called B-cell stimulating factor-2, may have an important role in antibody-mediated diseases, including those in restricted compartments of the body. Interleukin-6 is present in the aqueous humor of 63% of patients with uveitis.[21] This cytokine is also detected in the synovial fluid of patients with active rheumatoid arthritis,[22-24] in which interleukin-6 levels correlate with disease activity.[24]

Several tumors, such as cardiac myxomas and cervical carcinomas, produce interleukin-6. Patients with such tumors have hypergammaglobulinemia and multiple autoantibodies that disappear from the serum after surgical removal of the tumor.[25] Unregulated production of interleukin-6 might be responsible for autoantibody production in these patients.

The interleukin-6 we detected in the vitreous from patients with proliferative diabetic retinopathy could be involved in deposits of immunoglobulins in the walls of newly formed preretinal vessels.[2] Biopsies of the pars plana in proliferative diabetic retinopathy demonstrate immunoglobulin deposits at the level of the pigmented epithelium[3] and the preretinal membranes show extensive immunoglobulin deposits in the connective stroma and within the vascular walls.[4] In addition to increased intraocular interleukin-6 and ocular deposits of immunoglobulin, patients with type I diabetes mellitus have autoantibodies that are directed against a variety of pancreatic and nonpancreatic antigens. Moreover, the frequency of other autoimmune diseases is higher in diabetic patients than in the normal population.[26]

We have also found interleukin-6 in the vitreous from four patients with proliferative vitreoretinopathy (13.7 ± 4.7 pg/ml) (Reder, A. T., Abu El Asrar, A. M., and Maimone, D., unpublished data, 1991). In this disease also, immunoglobulin and complement deposits are seen at the level of the pigmented epithelium.[27] However, the disease mechanism differs from proliferative diabetic retinopathy, for there is metaplasia of the retinal pigment epithelium without vascular proliferation.

A pathogenetic role could be envisaged in proliferative retinopathy for tumor necrosis factor-α, possibly with a synergistic effect from interleukin-1β.[28] Tumor necrosis factor-α and interleukin-1β induce angiogenesis in ocular

interleukin-1β induce angiogenesis in ocular tissues[5,6] and proliferation of glial cells[7,8] and fibroblasts. We did not detect tumor necrosis factor-α in any of the vitreous samples we examined. Tumor necrosis factor-α clears rapidly from the circulation.[29] Similar rapid clearance or degradation of proteins in the eye could have hampered the detection of this cytokine in our study.[30]

Interleukin-1β was detected in seven of 16 vitreous samples from patients with proliferative diabetic retinopathy. Interleukin-1β, however, was also present in four of ten aqueous humor samples from normal control subjects. Normal aqueous humor contains a remarkably consistent spectrum of proteins, including immunoglobulin, albumin, and lower molecular weight proteins.[17] The pattern does not reflect serum proteins. The interleukin-1 in the aqueous and vitreous may have been synthesized within these compartments, for serum interleukin-1 was undetectable. Finally, surgical trauma to the iris markedly increases protein levels in the aqueous.[17] Our samples were obtained with exquisite care and trauma was unlikely. It is also possible that interleukin-6 down-regulates production of tumor necrosis factor-α and to some extent interleukin-1β in the eyes of patients with proliferative diabetic retinopathy.[31]

In previous immunopathologic studies, class II major histocompatibility complex antigen expression was noted in the pigmented epithelium,[3] as well as on many cells in the preretinal membranes[4] from patients with proliferative diabetic retinopathy. Interferon-γ is a potent inducer of class II antigen expression on a variety of epithelial cells in vitro,[11-13] and activates retinal pigmented epithelial cells, which allows them to present antigens.[32] Interferon-γ is detected in the vitreous of patients with acquired immunodeficiency syndrome retinitis[33] and sympathetic ophthalmia[34] and could amplify proliferative retinopathy. In our study, however, we failed to detect interferon-γ in the vitreous samples. We cannot exclude the possibility that small amounts of interferon-γ, not detectable with our ELISA system at the time of sampling, were present in the vitreous from patients with proliferative diabetic retinopathy. In this regard, the synovial fluid of patients with rheumatoid arthritis contains little or no interferon-γ, despite class II major histocompatibility complex antigen expression by the synovial cells.[35] This suggests that factors other than interferon-γ may be responsible for class II major histocompatibility complex antigen expression in localized compartments.

We found that detectable levels of interleukin-6 in vitreous samples from patients with proliferative diabetic retinopathy, and interleukin-6 levels correlate with clinically detectable ocular disease activity. The presence of interleukin-6 may account for the well-established finding of immunoglobulin deposition in ocular tissues. Our data suggest that an inflammatory reaction may further exacerbate disease severity in eyes of patients with proliferative retinopathy. Therefore, the use of anti-inflammatory drugs or cytokine antagonists before, during, and after surgical intervention warrants further evaluation.

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Results of Intraoperative 5-Fluorouracil Supplementation on Trabeculectomy for Open-angle Glaucoma

M. Fran Smith, M.D., Mark B. Sherwood, M.D., J. William Doyle, M.D., and Peng T. Khaw, M.D.

The success rate of filtration surgery has been increased by the postoperative subconjunctival injection of 5-fluorouracil, a potent antimetabolite. However, the optimal route of administration has not been determined. Trabeculectomy was performed on one eye each of 14 patients. Topical 5-fluorouracil was applied intraoperatively (50 mg/ml for five minutes) and subconjunctival 5-fluorouracil was injected postoperatively (an average of 5.8 injections) (mean total dose, 29 mg). Seven of the 14 eyes had primary open-angle glaucoma, and seven eyes had open-angle glaucoma with either uveitis, aphakia, or previous failed trabeculectomy. Mean preoperative intraocular pressure was 24.7 mm Hg during treatment with an average of three antiglaucoma medications, and mean final intraocular pressure was 11.9 mm Hg during treatment with an average of 0.2 medication. Thirteen of 14 eyes (93%) had final intraocular pressure of 18 mm Hg or less. Mean follow-up was 6.4 months (range, four to nine months). No remarkable complications occurred. Visual acuity remained stable in 13 of 14 eyes (93%). Intraoperative 5-fluorouracil may be a helpful adjunct in achieving low final intraocular pressure after trabeculectomy.

A FLUORINATED PYRIMIDINE ANALOGUE, 5-fluorouracil, acts as a potent antimetabolite by competitively inhibiting thymidylate synthetase and cell division. Animal studies demonstrated decreased fibroblast proliferation and scarring after filtration surgery when 5-fluorouracil was administered postoperatively.[1] Postoperative subconjunctival 5-fluorouracil injections in humans increased the success rate of filtration surgery in complicated cases.[2-7] Additionally, low-dose postoperative 5-fluorouracil treatment regimens are associated with lower final intraocular pressures in initial operations for open-angle glaucoma.[8,9] However, subconjunctival injections are uncomfortable for the patient and inconvenient for the physician. The optimal time and route of 5-fluorouracil administration has not been determined. Topical 5-fluorouracil causes excess corneal toxicity,[10,11] and slow-release preparations have not been uniformly successful.[12-15] Recent cell culture work showed prolonged effects on fibroblast proliferation from a single five-minute exposure to 5-fluorouracil.[16] We also demonstrated enhanced effectiveness of 5-fluorouracil in rabbits, when combined intraoperative and postoperative 5-fluorouracil was used (Doyle, J. W., Sherwood, M. B., Khaw, P. T., and McGrory, S., unpublished data, 1992).

In the current study, we used intraoperative 5-fluorouracil administration, followed by low-dose postoperative subconjunctival 5-fluorouracil injections, in patients with primary open-angle glaucoma and patients with complicated open-angle glaucoma.

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From the Department of Ophthalmology, University of Florida College of Medicine, Gainesville, Florida. This study was supported in part by an unrestricted departmental grant from Research to Prevent Blindness, Inc., New York, New York. This study was presented as a poster at the annual meeting of the Association for Research in Vision and Ophthalmology, Sarasota, Florida, May 8, 1992.

Reprint requests to Mark B. Sherwood, M.D., Department of Ophthalmology, University of Florida, P.O. Box 100284 JHMHC, Gainesville, FL 32610-0284.

Patients and Methods

We reviewed the charts of patients who underwent trabeculectomy with intraoperative 5-fluorouracil application by one of us (M.B.S.) and who had at least four months of follow-up. Fourteen eyes of 14 patients were identified. Seven patients had advanced primary open-angle glaucoma and underwent initial trabecu-

lectomy. The other seven patients had complicated glaucoma (pseudophakic or aphakic patients, uveitic patients, or patients in whom previous trabeculectomy had failed). Patients were aged between 26 and 78 years (mean, 56 years); eight of 14 patients (57%) were white, and six of 14 (43%) were black; eight of 14 (57%) were men.

All trabeculectomies were performed in a similar fashion. A limbal-based conjunctival and Tenon's flap was developed, and after hemostasis was obtained, a rectangular partial-thickness scleral flap was made. At this point, before entering the anterior chamber, precut cellulose sponges soaked in 5-fluorouracil (50 mg/ml) were placed under and over the scleral flap, and subconjunctivally (Fig. 1). The sponges were left in position with the overlying tissues approximated to them for five minutes. After five minutes, the sponges were removed and the site was rinsed thoroughly with approximately 200 ml of balanced salt solution. Then a paracentesis tract was made with a 25-gauge needle. The internal scleral block was removed, and the scleral flap was reapproximated over the sclerostomy with two or more releasable sutures. Tenon's capsule and conjunctival layers were closed in two layers with 8-0 polyglactin on a BV needle. Subconjunctival injections of gentamicin (20 mg) and methylprednisolone (20 mg) were given.

Postoperative treatment included topical antibiotic, cycloplegic, and corticosteroid eyedrops. An average of five (range, four to seven) subconjunctival injections of 5-fluorouracil (5 mg in 0.2 ml of balanced salt solution) were given postoperatively to the eyes with primary open-angle glaucoma, and an average of 6.6 (range, two to ten) injections were given to the eyes with more complicated glaucoma. These injections were given over the first two postoperative weeks. The subconjunctival 5-fluorouracil was withheld if a corneal epithelial defect developed, or a Seidel-positive aqueous leak from bleb or incision occurred. The other end point for subconjunctival injections was based on bleb appearance.

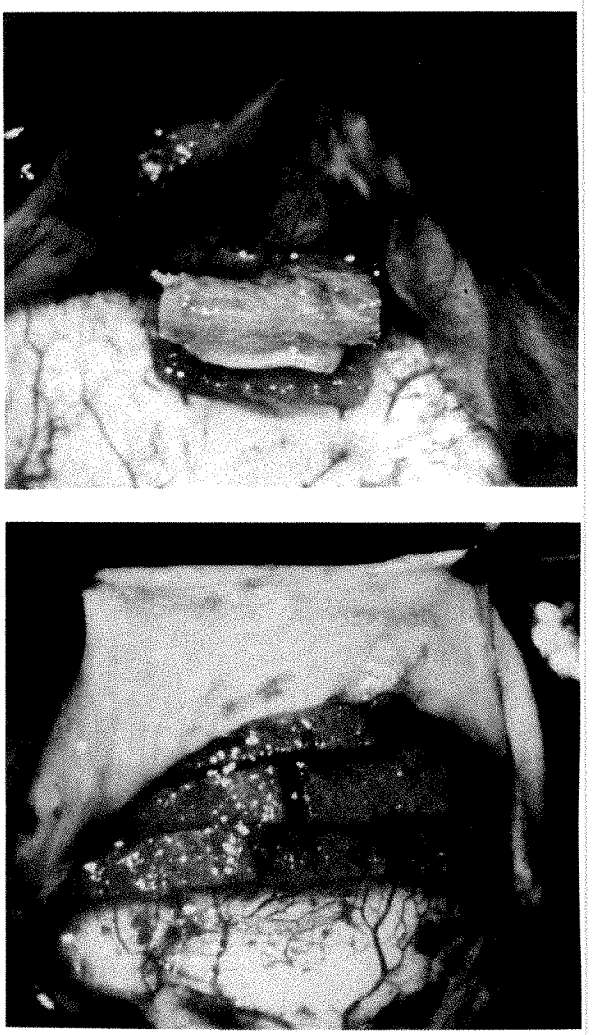


Fig. 1 (Smith and associates). Top, Placement of trimmed (two) cellulose sponges soaked in 5-fluorouracil (50 mg/ml) under and over the partial-thickness scleral flap. Bottom, Placement of additional (five to six) trimmed sponges soaked in 5-fluorouracil (50 mg/ml) in the subconjunctival space.

Results

Preoperative intraocular pressure for all 14 eyes averaged 24.8 mm Hg (range, 19 to 45 mm Hg) during treatment with a mean of three antiglaucoma medications. The subgroup of seven eyes with primary open-angle glaucoma (on which initial trabeculectomy was performed) had an average initial intraocular pressure of 23.0 mm Hg (range, 19 to 33 mm Hg). Initial intraocular pressure for the seven eyes with complicated glaucoma averaged 26.1 mm Hg (range, 19 to 25 mm Hg) (Table).

If treatment success is defined as a final intraocular pressure of 18 mm Hg or less, treatment was successful in 13 of 14 eyes (93%) (Fig. 2). Eleven of these 13 eyes required no additional medications; two eyes were being treated with one medication each. One treatment failure occurred after six months of follow-up in a

TABLE
PREOPERATIVE AND POSTOPERATIVE FINDINGS

	MEAN INTRAOCULAR PRESSURE (MM HG)		MEAN NO. OF MEDICATIONS		NO. OF PATIENTS WITH FINAL INTRAOCULAR PRESSURE ≤ 18 MM HG	MEAN FOLLOW-UP (MOS)
	PREOP-ERATIVE	POSTOPERATIVE (FINAL)	PREOP-ERATIVE	POSTOPERATIVE (FINAL)		
All eyes (N=14)	24.8	11.9	3	0.2	13	6.4
Eyes with primary open-angle glaucoma (N=7)	23.0	9.3	3	0	7	5.9
Eyes with complicated glaucoma (N=7)	26.1	14.6	3	0.4	6	7.0

60-year-old white man status post multiple intraocular procedures, including intracapsular cataract extraction, vitrectomy, and trabeculectomy. His intraocular pressure at last examination was 22 mm Hg during treatment with one medication.

Final mean intraocular pressure for all eyes was 11.9 mm Hg (range, 4 to 22 mm Hg) during treatment with a mean of 0.2 (range, zero to one) medication. The seven eyes with primary open-angle glaucoma had an average final intraocular pressure of 9.3 mm Hg (range, 4 to 15 mm Hg) with no medical treatment. The subgroup of seven eyes with complicated glaucoma had an average final intraocular pressure of 14.6 mm Hg (range, 9 to 22 mm Hg) during treatment with a mean of 0.4 (range, zero to one) medication. Eleven of 14 eyes (79%) were not being treated with medication at this most recent visit. The mean follow-up for these eyes was 6.4 months (range, four to nine months).

Visual acuity remained stable (plus or minus one Snellen line) in 13 of 14 eyes (93%) (Fig. 3). One eye lost four Snellen lines of visual acuity over the first six postoperative months, secondary to progression of cataract. This patient had aqueous misdirection after trabeculectomy, with shallow anterior chamber for three weeks; there was resolution with medical therapy. No cases of hypotony maculopathy with loss of visual acuity were seen, though one eye had a final intraocular pressure of 4 mm Hg.

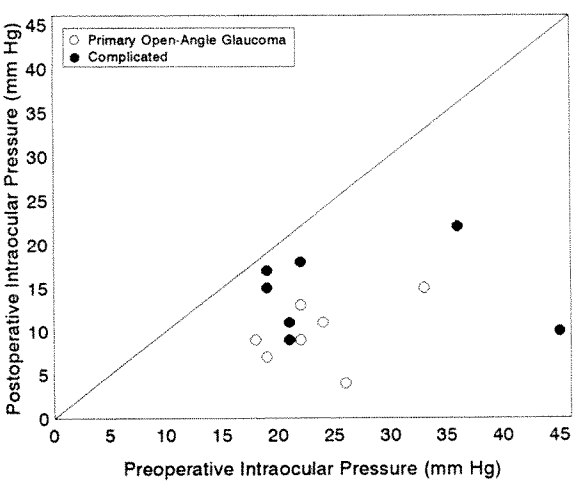


Fig. 2 (Smith and associates). A comparison of preoperative to postoperative intraocular pressures in the seven eyes with primary open-angle glaucoma, and the seven eyes with complicated glaucoma, treated with intraoperative and postoperative 5-fluorouracil.

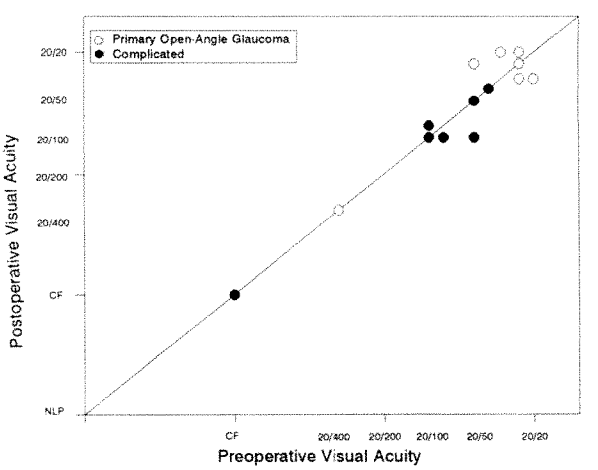


Fig. 3 (Smith and associates). A comparison of preoperative to postoperative visual acuity in the seven eyes with primary open-angle glaucoma, and the seven eyes with complicated glaucoma, treated with intraoperative and postoperative 5-fluorouracil.

Minor complications occurred in five of 14 eyes (36%). These complications included two epithelial defects, which promptly resolved after discontinuation of 5-fluorouracil injections, and a case of spontaneously resolving choroidal effusion. There was one central bleb leak on postoperative day 8, which resolved with patching for one day. As noted previously, there was also one case of aqueous misdirection that resulted in cataract progression; this was the only complication that resulted in marked loss of visual acuity (more than one Snellen line). No major complications requiring repeat trabeculectomy occurred. No scleral or corneal ulceration was noted.

Discussion

The effectiveness of 5-fluorouracil, a potent antimetabolite, has been demonstrated in several studies.[2-9] Initial trabeculectomy in eyes with primary open-angle glaucoma has a high success rate with lower final intraocular pressures when postoperative, subconjunctival low-dose (range, 10 to 55 mg; mean, 32 mg) 5-fluorouracil is used.[8,9] Trabeculectomy in eyes with complicated glaucoma has an increased success rate when a moderate dose (approximately 50 mg) of postoperative subconjunctival 5-fluorouracil is used.[2-7] However, the frequent subconjunctival injections may be unpleasant for the patient, inconvenient for the surgeon, and impossible to provide if certain complications intervene, or if the patient is lost to follow-up.

Intraoperative application of the antimetabolite, mitomycin C, has been studied in animals and humans.[17-19] Direct intraoperative application of 5-fluorouracil has several theoretical advantages. Intraoperative 5-fluorouracil application is easy and convenient for both patient and surgeon. The target tissues are immediately exposed to a maximum 5-fluorouracil concentration at the time of the inflammatory stimulus. Further, drug toxicity to other surrounding tissues, such as the cornea, should be minimized.

Our recent cell culture work demonstrated prolonged inhibition of human ocular fibroblast proliferation after a single 5-fluorouracil exposure.[16] As compared with fibroblasts exposed to mitomycin C (0.1 mg/ml) in which growth is arrested for 36 days, fibroblasts exposed to 5-fluorouracil (25 mg/ml) begin to reproliferate after about 12 days.[16] Because late bleb leaks and hypotony are a concern with mitomycin C, the use of an intraoperative agent such as 5-fluorouracil, which has a shorter lasting effect on the fibroblasts, may be a viable alternative for many patients. Our rabbit studies demonstrated a positive effect on bleb longevity when 5-fluorouracil was used intraoperatively, both alone or in conjunction with postoperative subconjunctival 5-fluorouracil injections. In theory, the greater reversibility of a five-minute intraoperative exposure to 5-fluorouracil (50 mg/ml) compared to mitomycin C may reduce the incidence of impaired conjunctival healing. The risk of bleb leaks would also be reduced, while still allowing titration of antifibroblast effect according to bleb appearance, via postoperative 5-fluorouracil injections. This preliminary experience with intraoperative 5-fluorouracil in 14 human eyes is promising. Final intraocular pressures were low, and the short-term success rate was high. We gave one-third fewer 5-fluorouracil injections in the eyes with complicated glaucoma, compared to the dosage we routinely use in such eyes (ten injections over a two-week period), yet maintained a good success rate. It may be possible to reduce 5-fluorouracil dosage still further, especially in eyes with primary open-angle glaucoma on which initial trabeculectomy is being performed. Possibly, treatment with only intraoperative administration of 5-fluorouracil may be successful in eyes with primary open-angle glaucoma that do not require exceptionally low postoperative intraocular pressures.

Firm conclusions regarding the future role of intraoperative 5-fluorouracil cannot be drawn from our pilot study results. Our study lacked a control group, and treatment is successful in many patients after a filtering operation without any antimetabolite use. This mode of 5-fluorouracil delivery did not result in any hypotony that caused loss in visual acuity or other complication, and yet was associated with encouraging intraocular pressure results. Future prospective studies with larger numbers are needed to determine the best timing and mode of delivery of 5-fluorouracil. A study investigating the use of intraoperative 5-fluorouracil alone vs a control group, as well as a study comparing the use of intraoperative combined with postoperative 5-fluorouracil vs postoperative 5-fluorouracil alone would be helpful. Our study suggests that intraoperative adjunctive use of 5-fluorouracil is safe, and may decrease

the need for postoperative 5-fluorouracil injections.

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OPHTHALMIC MINIATURE

To suppose that the eye with all its inimitable contrivances for adjusting the focus to different distances, for admitting different amounts of light, and for the correction of spherical and chromatic aberration, could have been formed by natural selection, seems, I freely confess, absurd in the highest degree.

Charles Darwin, "Organs of Extreme Perfection and Complication,"
Origin of the Species
New York, P. F. Collier & Son, 1909, p. 181

Intravitreal Foscarnet for Cytomegalovirus Retinitis in a Patient With Acquired Immunodeficiency Syndrome

Manuel Díaz-Llopis, M.D., Enrique Chipont, M.D., Santiago Sanchez, Pharm.D., Enrique España, M.D., Amparo Navea, M.D., and Jose L. Menezo, M.D.

We treated a patient who had acquired immunodeficiency syndrome and cytomegalovirus retinitis of the left eye. After anesthetic had been topically administered, the patient received intravitreal injections of 1,200 μg of foscarnet. Plasma and vitreous foscarnet levels were measured by high-performance liquid chromatography. Systemic absorption of the drug was not evident. Elimination half-life from the vitreous after one injection was 54.0 hours. Vitreous levels remained above the mean 50% inhibition value for cytomegalovirus for approximately 56 hours and above the mean inhibition value for human immunodeficiency virus for approximately 241 hours. The patient's visual acuity improved from 20/30 to 20/25 in the left eye. Ophthalmoscopy showed the retinal lesion to have become inactive, and no reactivation occurred during the follow-up period of more than four months. The drug was well tolerated and no retinal toxicity was evident. We suggest an induction treatment regimen of two injections weekly for three weeks, followed by a maintenance treatment regimen of one injection weekly.

CYTOMEGALOVIRUS RETINITIS, the major cause of loss in visual acuity in acquired immunodeficiency syndrome (AIDS), develops in between 12% and 46% of patients.[1-5]

Only two virostatic drugs, ganciclovir and foscarnet, have been effective in cytomegalovirus retinitis when administered systemically. Induction doses of either of these drugs halt progression of the retinitis in between 87% and 97% of cases,[6-15] though lesions often reactivate during maintenance therapy in between 30% and 53% of cases.

The high incidence of side effects, particularly myelotoxicity, associated with intravenous administration of ganciclovir results in discontinuation of treatment in between 13% and 38% of patients.[6,9-11,16] Intravitreal administration has been an effective alternative in these patients,[17,18] though Yoshizumi and associates[19] found retinal toxicity after repeated intravitreal injection of doses of ganciclovir (200 μg) previously considered to be therapeutic.

Foscarnet (trisodium phosphonoformate hexahydrate), as compared with ganciclovir, has the double advantage of being active against human immunodeficiency virus (HIV)[20] and of allowing concomitant treatment with zidovudine,[21] a drug that has been shown to improve survival in these patients.[22] The principal drawback of intravenous foscarnet is its high renal toxicity.[21] Renal toxicity is seen in approximately 46% of patients during treatment and precludes use of the drug in patients whose serum creatinine level is more than twice the normal value.

We treated a man who had AIDS and cytomegalovirus retinitis of the left eye. A history of intolerance to acyclovir and the presence of advanced renal failure meant that ganciclovir could not be given by any route and that foscarnet could not be given intravenously. Because a study by She, Peyman, and Schulman[23] on rabbits showed absence of retinal toxicity after intravitreal doses of up to 1,000 μg of foscarnet, we decided, because of the absence of any therapeutic alternative and on a compassionate basis, to administer foscarnet to this patient by intraocular injection to study the pharmacokinetics, possible toxicity, and potential effectiveness of the substance.

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From the Departments of Ophthalmology (Drs. Díaz-Llopis and Menezo), Microbiology (Dr. Chipont), Pharmaceutical Services (Dr. Sanchez), Internal Medicine (Dr. España), and Pathology (Dr. Navea), La Fe Hospital, University of Valencia School of Medicine, Valencia, Spain. This study was supported in part by Fondo de Investigaciones Sanitarias de la Seguridad Social grant No. 92/0403 (Spain).

Reprint requests to Manuel Díaz-Llopis M.D., Pza. San Agustin 3-D-54, 46002 Valencia, Spain.

Case Report

A 37-year-old homosexual man was classified in Group IV according to the Centers for Disease Control criteria for the classification of HIV infections.[24] The only clinical manifestation of AIDS before the development of cytomegalovirus retinitis had been an episode of *Pneumocystis carinii* pneumonia seven months previously.

On May 10, 1991, a paracentral scotoma was found in the patient's left eye. Visual acuity was R.E.: 20/20 and L.E.: 20/30. Ophthalmoscopy disclosed a zone of necrotizing retinitis with hemorrhages and vasculitis along the length of the superior temporal vasculature of the left eye. Urine cultures were positive for cytomegalovirus.

The patient had a history of an erythematous, pruritic reaction to acyclovir ointment that was applied six years previously for herpes simplex. This history and the presence of chronic renal failure with creatinine levels of more than 250 μmol/l precluded the use of ganciclovir by any route and of foscarnet by the intravenous route.

After obtaining permission from the clinical trials and ethics committee of our hospital and the informed consent of the patient, we commenced treatment on a compassionate basis with intravitreal foscarnet. The fundus was photographed before and during the course of treatment (Figs. 1 and 2).

Material and Methods

A solution of sterile isotonic foscarnet (pH 7.4) for intravenous infusion (Foscavir, Astra Laboratories, Södertälje, Sweden) was passed through a 0.22-μm filter before injection. Each milliliter of the solution contained 24 mg (80 μmol) of foscarnet trisodium hexahydrate, hydrochloric acid for injection as much as desired, and water for injection as much as desired. After anesthetic had been administered topically, 0.05 ml of this solution containing 1,200 μg (4 μmol) of foscarnet trisodium hexahydrate was injected undiluted into the inferotemporal quadrant, 4 mm from the corneoscleral limbus, by using a 30-gauge needle in an outpatient regimen described previously.[25]

Foscarnet was injected intravitreally into the left eye six times at 72-hour intervals during the first 17 days, after which one injection was given weekly until the patient died. Plasma samples for analysis of foscarnet concentration were taken 24, 48, and 72 hours after the first injection. Two samples of vitreous were ob-

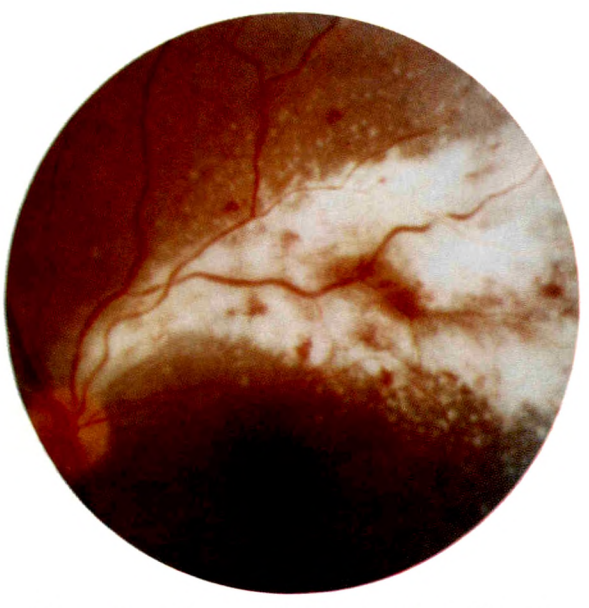


Fig. 1 (Díaz-Llopis and associates). Active cytomegalovirus retinitis along the length of the superior temporal vasculature of the left eye.



Fig. 2 (Díaz-Llopis and associates). Detail of the area temporal to the macula. Note considerable resolution of retinitis four months after treatment with intravitreal foscarnet.

tained from the left eye: the first 23¼ hours after the first injection, and the second 49½ hours after the sixth injection. The vitreous aspirations were performed with the patient under retrobulbar anesthesia and with aseptic surgical conditions by using a 21-gauge needle with previous sclerotomy and subsequent suture. All plasma and vitreous samples were immediately frozen and kept at −20 C until analysis via a simple, high-performance liquid chromatography assay with electrochemical detection[26] and a lower limit of detection of 33 μmol/l.

When the patient died his eyes were enucleated and fixed in 10% formaldehyde and glutaraldehyde solution, were dehydrated in a graded series of alcohol, were embedded in paraffin, and were sectioned with a microtome. The sections were stained with hematoxylin and eosin and examined with light microscopy. Previously, vitreous samples were obtained for a postmortem antigenic study and culture of vitreous aspirate for cytomegalovirus and HIV.

Intraocular foscarnet concentration vs time since injection, real volume of distribution, and elimination half-life from the vitreous were computed by using a one-compartment model with a nonlinear regression line.[27]

Results

All the plasma samples taken during treatment were negative for foscarnet, indicating absence of any notable degree of systemic absorption of the drug. Similarly, serum creatinine or blood urea nitrogen concentrations did not change notably during treatment.

The concentration of foscarnet in the vitreous after injection of 4 μmol in 0.05 ml was 409 μmol/l at 23¼ hours after the first injection and 292 μmol/l at 49½ hours after the sixth injection. The elimination half-life of foscarnet from the vitreous was approximately 54 hours. The real volume of distribution of the drug was 7.2 ml.

The treatment was well tolerated and toxicity was not evident. The media remained clear. Ophthalmoscopy of the left eye showed resolution of the necrotizing retinitis with transformation into an atrophic geographic zone with pigmentary changes, with persistence of some hemorrhages and nonedematous white areas (Fig. 2). After three weeks, visual acuity in the left eye had improved from 20/30 to 20/25, and the scotoma became almost clinically undetectable and remained unchanged until the death of the patient. After the series of two injections weekly for three weeks, the treatment regimen was changed to one injection weekly for maintenance. At no time during the total follow-up period of four months and one week was there any ophthalmoscopic evidence of reactivation of the lesion. The patient died from another episode of *P. carinii* pneumonia after having received a total of 21 intravitreal injections. The postmortem antigenic study was nonreactive and cultures of vitreous aspirate were negative for HIV and cytomegalovirus. On transverse incision above the optic nerve, there was a focus of retinal necrosis along the length of the superior temporal vasculature of the left eye. On microscopy, the retina within the lesion was severely scarred and thin. At the margin of the region of scarring, there were a few typical cells containing both nuclear and cytoplasmic inclusions. The underlying pigment epithelium was disorganized and focally missing. A few scattered lymphocytes were noted in the retina and in the underlying choroid. Light microscopy of unaffected tissues demonstrated no abnormalities.

Discussion

The proven development of resistance in up to 38% of patients with AIDS treated for long periods with systemic ganciclovir for cytomegalovirus infection[28] imposes the need for new therapeutic approaches.

One of the main problems with the use of antiviral agents for ocular infections is their poor intraocular penetration. Our pharmacokinetic study showed that intravitreally administered foscarnet avoided the blood-retinal barrier and achieved high nontoxic levels in the vitreous. The elimination half-life of foscarnet from the vitreous of approximately 54 hours after intravitreal injection is thus far greater than the plasma half-life of the substance after intravenous administration (that is, between one and three hours).[21] The apparent volume of distribution of intravitreal foscarnet was 7.2 ml. This greater-than-normal volume for human vitreous may be explained by uptake of the substance in the retina. The mean 50% inhibition value of foscarnet for most strains of cytomegalovirus that have been isolated from humans is approximately 271 μmol/l,[29] whereas

that for the HIV ranges from 10 to 25 μmol/l.[21]

On the basis of the currently available pharmacokinetic data, computer simulation suggests that after a single intravitreal injection of 1,200 μg, the concentration of foscarnet in the vitreous would remain above the mean 50% inhibition value for cytomegalovirus for approximately 56 hours. The concentration of foscarnet in the vitreous would also remain above the mean 5% inhibition value for HIV for approximately 241 hours. Henry and associates[17] calculated that after intravitreal injection of a 200-μg dose, the concentration of ganciclovir in the vitreous would remain above the mean 50% inhibition value for cytomegalovirus for 62 hours.

As the number of intravitreal injections required for induction and maintenance treatment is the same with foscarnet as with ganciclovir, the frequency of complications of the intravitreal technique (endophthalmitis, retinal detachment, vitreal hemorrhage, optic atrophy, and the like)[25] would be expected to be the same with both substances. Nevertheless, foscarnet has a number of potential advantages. First, the pH of the foscarnet solution (7.4) is more physiologic than that (10.1) of the ganciclovir solution. Second, the amount of liquid to be injected is smaller with foscarnet treatment (0.05 ml with foscarnet as compared to 0.1 ml with ganciclovir), which implies a lower risk of reflux of liquid and perhaps of affecting the circulation of the central retinal artery. Third, foscarnet is active against HIV. This activity may be important in terms of ocular conditions such as iridocyclitis[30] and retinal dysfunction,[31] postulated to be direct manifestations of ocular HIV infection, and of dual infections of the retina with both cytomegalovirus and HIV.[32] The existence of dual infection of this type may explain the poor response to treatment of some cases of cytomegalovirus retinitis. The possibility of achieving therapeutic levels against both viruses with a single intraocular drug therefore would constitute an important additional advantage of foscarnet over ganciclovir.

The combination of foscarnet and ganciclovir has been demonstrated both in vitro and in vivo to exert a synergistic effect against cytomegalovirus.[33] Treatment of cytomegalovirus retinitis with macular involvement with a combination of intravitreally and intravenously administered antiviral drugs as suggested by Daikos and associates[34] would, in the frequent cases in which the patient is already being treated with intravenous ganciclovir, therefore be best achieved by adding intravitreal foscarnet rather than ganciclovir to the existing treatment regimen.

Our patient's retinitis became inactive after direct intravitreal administration of foscarnet twice weekly for three weeks, though ophthalmoscopic signs of residual activity persisted. Reactivation did not occur with the maintenance regimen of one injection weekly. On the basis of the pharmacokinetic data, we recommend that the interval between doses should not exceed one week. The absence of intraocular toxicity is evidenced by the patient's visual acuity remaining at 20/25 in the left eye throughout the follow-up period of more than four months.

The principal advantage of intravitreal as opposed to intravenous administration of foscarnet is the absence of systemic side effects, nephrotoxicity in particular.[14] In our patient, for example, the laboratory indices of renal failure showed no deterioration during treatment with intravitreal foscarnet, or any evidence of anemia, hypercalcemia, or hyperphosphatemia. However, intravitreal therapy is purely palliative, as it has no effect on the systemic cytomegalovirus infection. Therefore, although the infection did not become bilateral in our patient, a greater incidence of progression to bilateral cytomegalovirus retinitis and a poorer survival rate would be expected with intravitreal therapy.[9,18,25]

The data presented here are derived from one patient and must therefore be interpreted with caution. Also, future intraocular use of this drug may cause adverse reactions, toxicity, or complications. Nevertheless, we believe that intravitreal foscarnet is a worthwhile therapeutic alternative for cytomegalovirus retinitis in patients with AIDS.

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OPHTHALMIC MINIATURE

"Do not be afraid, missus," said Gideon, "this will cure Little Yellow Head's eyes." He stripped the leaves from the plant, leaving a small white fleshy root. Without even washing it, he put the root in his mouth, chewed it vigorously, and then held the spittle there while he took the child forcibly from Mrs. Farquar. He gripped Teddy down between his knees and pressed the balls of his thumbs into the swollen eyes, so that the child screamed and Mrs. Farquar cried out in protest: "Gideon, Gideon!" But Gideon took no notice. He knelt over the writhing child, pushing back the puffy lids till chinks of eyeball showed, and then he spat hard, again and again, into first one eye, and then the other. He finally lifted Teddy gently into his mother's arms and said: "His eyes will be better." But Mrs. Farquar was weeping with terror, and she could hardly thank him; it was impossible to believe that Teddy could keep his sight. In a couple of hours the swellings were gone; the eyes were inflamed and tender but Teddy could see.

Doris Lessing, "No Witchcraft for Sale," *Modern British Prose*
New York, Harcourt, Brace & World, 1969, pp. 180-181

Ultrastructural Findings in an Autopsy Eye From a Patient With Usher's Syndrome Type II

Eliot L. Berson, M.D., and Michael Adamian, B.A.

We studied an eye taken at autopsy from a 55-year-old woman with retinitis pigmentosa and partial deafness (Usher's syndrome type II). Two years before her death, her visual acuity was R.E.: 20/80 and L.E.: 20/50, and visual fields were constricted to a 30- to 40-degree diameter with a V_{4e} white test light. Both rods and cones were present across the retina except for areas of the midperiphery; remaining photoreceptors had shortened or disrupted outer segments, or both, and some cones had inclusion bodies in inner segments. In the macula, most of the connecting cilia of photoreceptors appeared abnormal, with either extra microtubules or an apparent disruption of the nexin link between doublet microtubules. The pigment epithelium was abnormal across the eye, with diminished apical microvilli and basal infoldings of the plasma membrane. Possible mechanisms by which abnormal cilia could lead to photoreceptor cell death are considered.

RETINITIS PIGMENTOSA affects 50,000 to 100,000 people in the United States. Some 10% of affected individuals have associated hearing loss, sometimes referred to as Usher's syndrome in recognition of the British ophthalmologist, C. H. Usher, who emphasized that this condition was recessively inherited.[1,2] Merin, Abraham, and Auerbach[3] subdivided Usher's syndrome into four types, with types I and II separated on the basis of severity of hearing loss at birth and status of vestibular function and types III and IV notable for other involvement of the central nervous system. Patients with Usher's syndrome type I typically have night blindness in the first or second decade, profound congenital deafness with unintelligible speech, and a history of late onset of walking with a persistent disorder of balance. Patients with Usher's syndrome type II have night blindness in the second to fourth decade, have a partial high-tone hearing loss with intelligible speech, and do not show a balance disorder.[4] We studied the ultrastructural findings in an eye taken at autopsy from a patient with retinitis pigmentosa and partial deafness, or Usher's syndrome type II.

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From the Berman-Gund Laboratory for the Study of Retinal Degenerations, Harvard Medical School, Massachusetts Eye and Ear Infirmary. This study was supported by specialized research center grant EY02014 from the National Eye Institute (Dr. Berson); and by a grant from the National Retinitis Pigmentosa Foundation, Baltimore, Maryland (Dr. Berson).

Reprint requests to Eliot L. Berson, M.D., Berman-Gund Laboratory, Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114.

Case Report

A 55-year-old-woman was first told she had retinitis pigmentosa at 46 years of age, around the time she noted the onset of night blindness and loss of peripheral field. She had a long-standing, high-tone hearing loss confirmed by audiometry, but no balance disorder according to her history. She had no family history of retinitis pigmentosa or deafness. Two years before her death her best-corrected visual acuity was R.E.: 20/80 and L.E.: 20/50, with constricted visual fields to the 15- to 20-degree isopter with a I_{4e} white test light and the 30- to 40-degree isopter with a V_{4e} white test light, clear lenses, cystoid changes in each macula, and intraretinal pigment in a bone spicule configuration around the periphery. She had a tendency to tritanopia on the Farnsworth D15 panel, had a final dark adaptation threshold increased 2 log units above normal to an 11-degree white test light fixated 7 degrees above the fovea in the Goldmann-Weekers dark adaptometer, and a barely detectable full-field electroretinogram with delayed cone b-wave implicit times. Fundus examination of each eye two years before her death showed a normal disk, cystoid changes in the central macula, and

attenuated retinal arterioles. Intraretinal bone spicule pigmentation could be seen around the periphery. The midperipheral fundus had a tigroid appearance in each eye.

The patient developed a metastatic carcinoma of the breast one year before her death. A mastectomy was performed and the patient was treated with radiation and chemotherapy. She received cyclophosphamide, methotrexate, 5-fluorouracil, and doxorubicin hydrochloride intermittently in the year before her death. She died from cardiac and respiratory arrest in association with her cancer.

The patient's eyes were removed within one hour after death; the left eye was immediately fixed in 1% formaldehyde and 2% glutaraldehyde for light and electron microscopy; the right eye was placed on ice and then subdivided two hours after death for biochemical analyses. These biochemical analyses were difficult to interpret because of loss of retinal cells and were therefore not reported.

Light microscopy was performed on representative sections of the entire left retina stained with methylene blue-azure II. Blocks from the fovea, parafovea, and midperiphery and far periphery along the horizontal meridian were then sectioned, stained with uranyl acetate and lead citrate, and examined with an electron microscope. Selected blocks were reoriented and cut transversely to examine photoreceptor cilia and evaluated only in those instances in which microtubules could be unambiguously counted; 16 images of these cilia were available for comparison with those from an eye taken at autopsy from a normal adult.

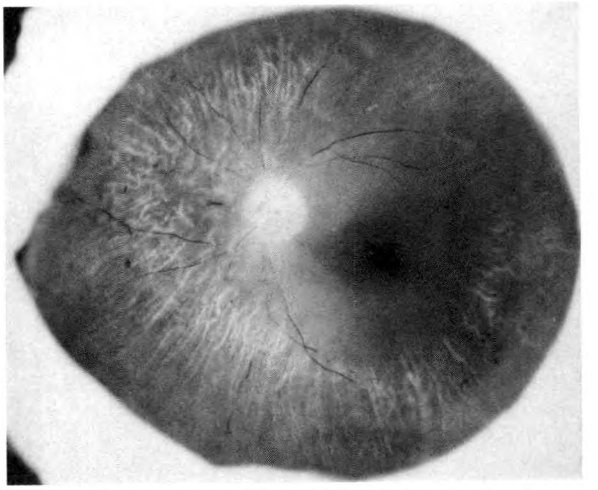


Fig. 1 (Berson and Adamian). Postmortem photograph of the left eye of a 55-year-old patient with Usher's syndrome type II. A prominent choroidal vessel pattern can be seen around the midperiphery; bone spicule pigment can be seen in the nasal and temporal quadrants.

Results

Gross examination of the left eye showed the relatively preserved macula as well as a tigroid appearance with sparse bone spicule pigment around the periphery (Fig. 1). On microscopic examination, the eye retained numerous photoreceptors but showed cystoid changes in Henle's fiber layer in the fovea (Fig. 2). In the

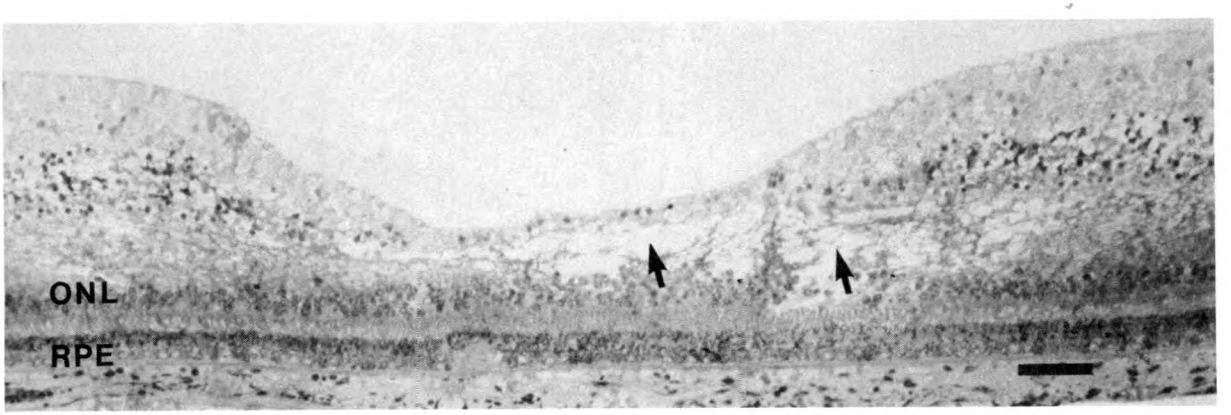


Fig. 2 (Berson and Adamian). Light micrograph from the macula shows cystoid changes in the fovea (arrows). The number of nuclei in the outer nuclear layer (ONL) appears normal or nearly normal in the fovea, but reduced in the parafovea. The retinal pigment epithelium (RPE) and inner retina retain normal architecture (bar = 50 μm).

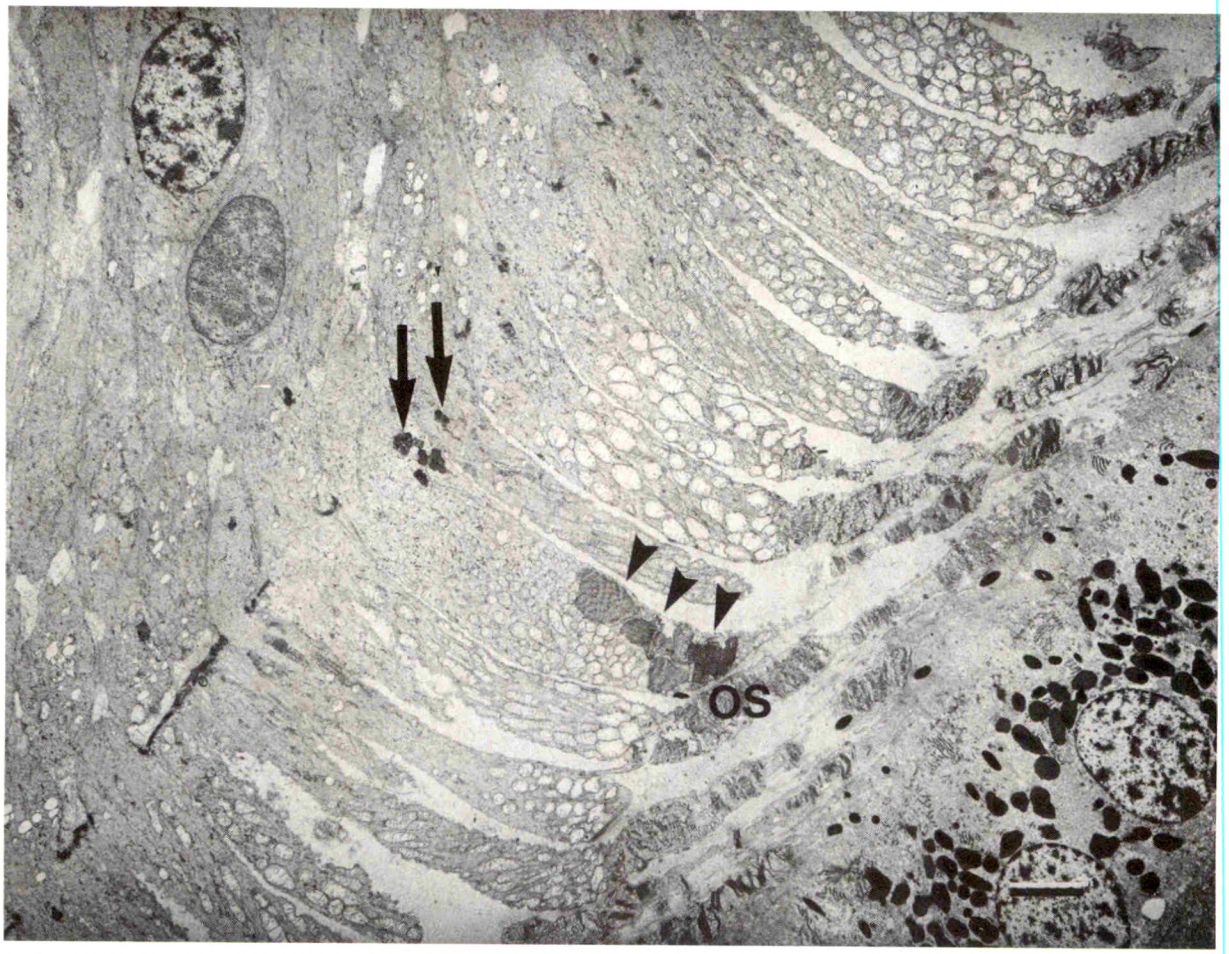


Fig. 3 (Berson and Adamian). Electron micrograph from the fovea discloses inclusion bodies (arrows) in both rods and cones and displaced outer segment disks (arrowheads) within a cone inner segment. Outer segments appear shortened and disrupted (bar = 4 μm).

parafovea, the outer nuclear layer showed an abnormal reduction in the number of nuclei; otherwise the retina and choroid appeared intact. Ultrastructural examination of the fovea showed that remaining cones and rods contained inclusion bodies in the inner segment located along the external limiting membrane, vacuolated mitochondria, and disorganized or distorted outer segments, or both (Fig. 3). Some outer segment material could be seen at the level of the inner segment.

In the region between the fovea and disk (Fig. 4), the number of photoreceptor nuclei was reduced to about 50% of normal, and outer segments of both rods and cones were distorted or shortened, or both. The interphotoreceptor matrix appeared abnormally electron dense. Some cone nuclei were displaced external to the external limiting membrane. The pigment epithelium contained melanin, melanolysosomes, and lipofuscin. The choriocapillaris appeared intact.

Temporal to the fovea, the outer nuclear layer was reduced in thickness by about 50%, and rod and cone outer segments were shortened and distorted. In the near midperiphery, the outer nuclear layer cell density was decreased precipitously, and inner segments for the most part were tightly apposed to the retinal pigment epithelium (Fig. 5).

The pigment epithelium in the region of the macula contained phagosomes within the apical processes (Fig. 6, top) or deep within the cells (Fig. 6, bottom). The apical microvilli and



Fig. 4 (Berson and Adamian). Electron micrograph from the nasal parafovea shows a single layer of rods and cones with shortened outer segments (OS). The interphotoreceptor matrix (asterisks) is dense and granular. Some cone nuclei are displaced distal to the outer limiting membrane (arrow) (bar = 5 μm).

basal infoldings appeared reduced or collapsed; these cells had a prominent rough endoplasmic reticulum and many melanolysosomes.

In the midperiphery, where the choroidal pattern was prominent on the gross specimen, only occasional photoreceptor cell bodies were seen as well as pigment-containing cells around retinal vessels that corresponded to the bone spicule pigmentation. In the far periphery, some cone photoreceptors were still visible, and cone inner segments abutted the retinal pigment epithelium. Pigment-containing cells were seen in the subretinal space and within the retina (Fig. 7); Bruch's membrane and the choriocapillaris appeared intact.

In addition to distorted outer segments, some photoreceptors in the macula had abnormal connecting cilia. Figure 8 shows a longitudinal section of a photoreceptor with a cross section through the connecting cilia at the level designated by the arrows. This cilium showed two extra microtubules (Fig. 8, inset) in contrast to a representative cross section through a normal connecting cilium (Fig. 9) that shows a circular configuration of nine regularly spaced doublet microtubules (Fig. 9, inset). Other cilia from the eye with Usher's syndrome type II had extra microtubules (Fig. 10, left) or an apparent disruption of the nexin link between doublet microtubules (Fig. 10, right). On the basis of 16 images of cilia from the region of the macula available to us for study, we determined that nine images of cilia appeared abnormal and

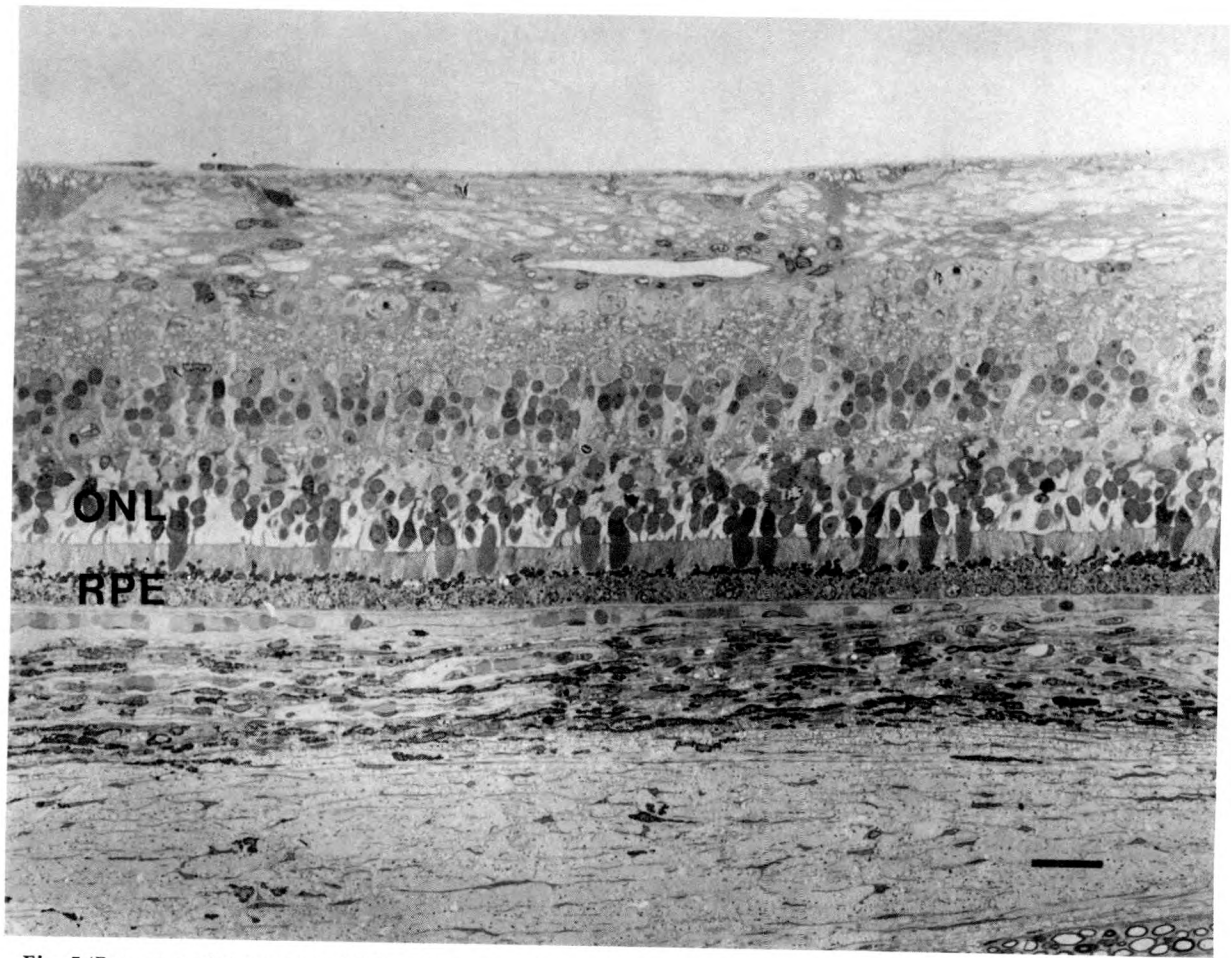


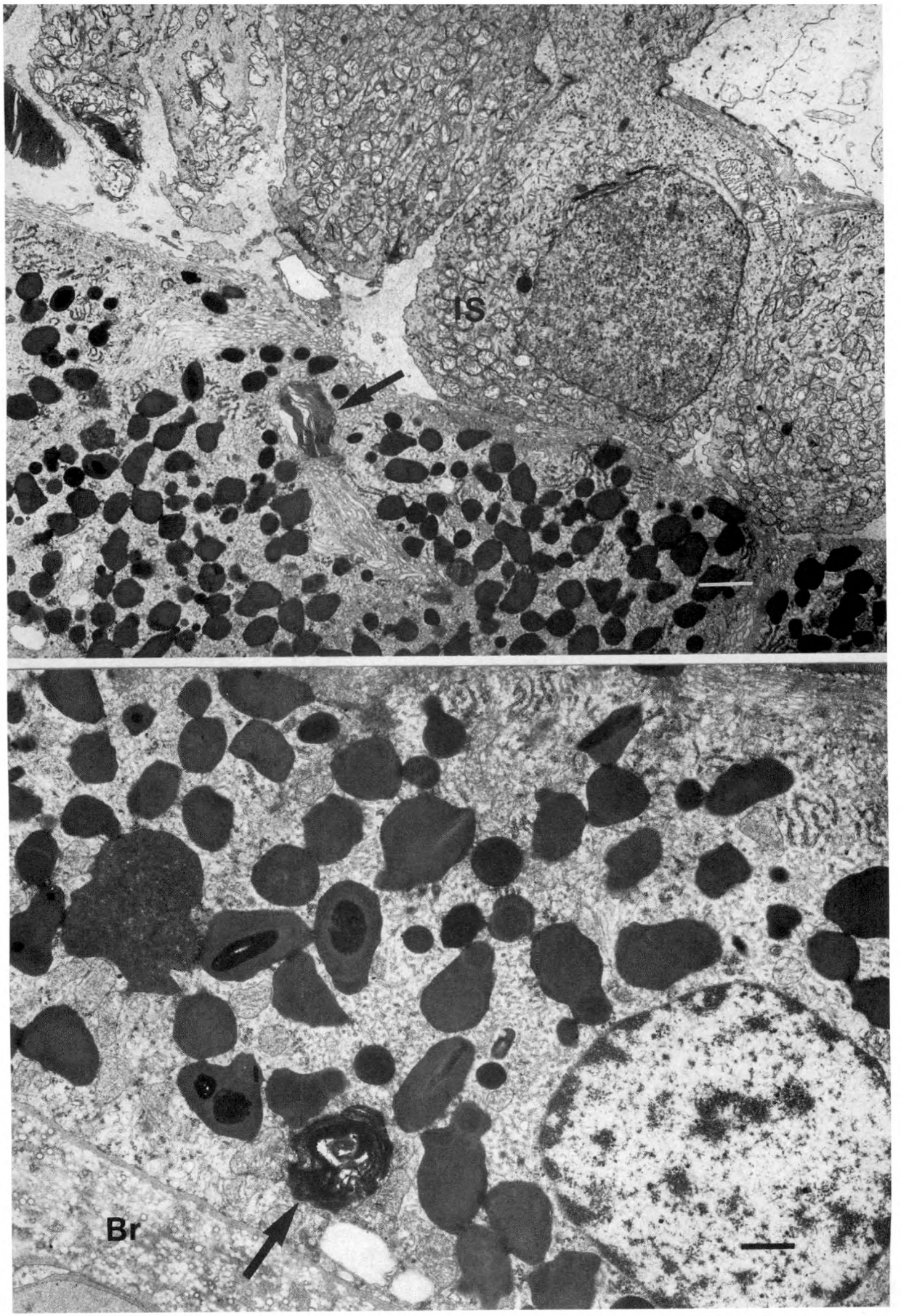
Fig. 5 (Berson and Adamian). Light micrograph from the temporal near periphery. The number of nuclei in the outer nuclear layer (ONL) is decreased. The retinal pigment epithelium (RPE) remains intact (bar = 30 μm).

seven images of cilia appeared normal; no abnormalities were seen in a comparable number of images from the normal eye taken at autopsy.

Discussion

We found that photoreceptors were reduced about 50% below normal in the central retina, were virtually absent in the midperiphery, and substantially reduced in the far periphery in this patient with Usher's syndrome type II. Clinical findings of elevated dark-adaptation thresholds, constricted visual fields, and reduced electroretinograms were compatible with the pathologic findings of rods and cones diminished in numbers with shortened outer segments in the macula and the virtual absence of both photoreceptor types in the periphery. The pigment epithelium contained phagosomes, lipofuscin, melanin, and melanolysosomes, but appeared to have diminished apical microvilli and basal infoldings while the cho-

Fig. 6 (Berson and Adamian). Retinal pigment epithelium in the macula shows phagosomes (arrows) within the apical portion (top) and basal portion (bottom) near Bruch's membrane (Br). A displaced photoreceptor nucleus can be seen in an inner segment (IS) abutting the pigment epithelium (top) (bars = 1 μm [top] and 2 μm [bottom]).


IS
Br

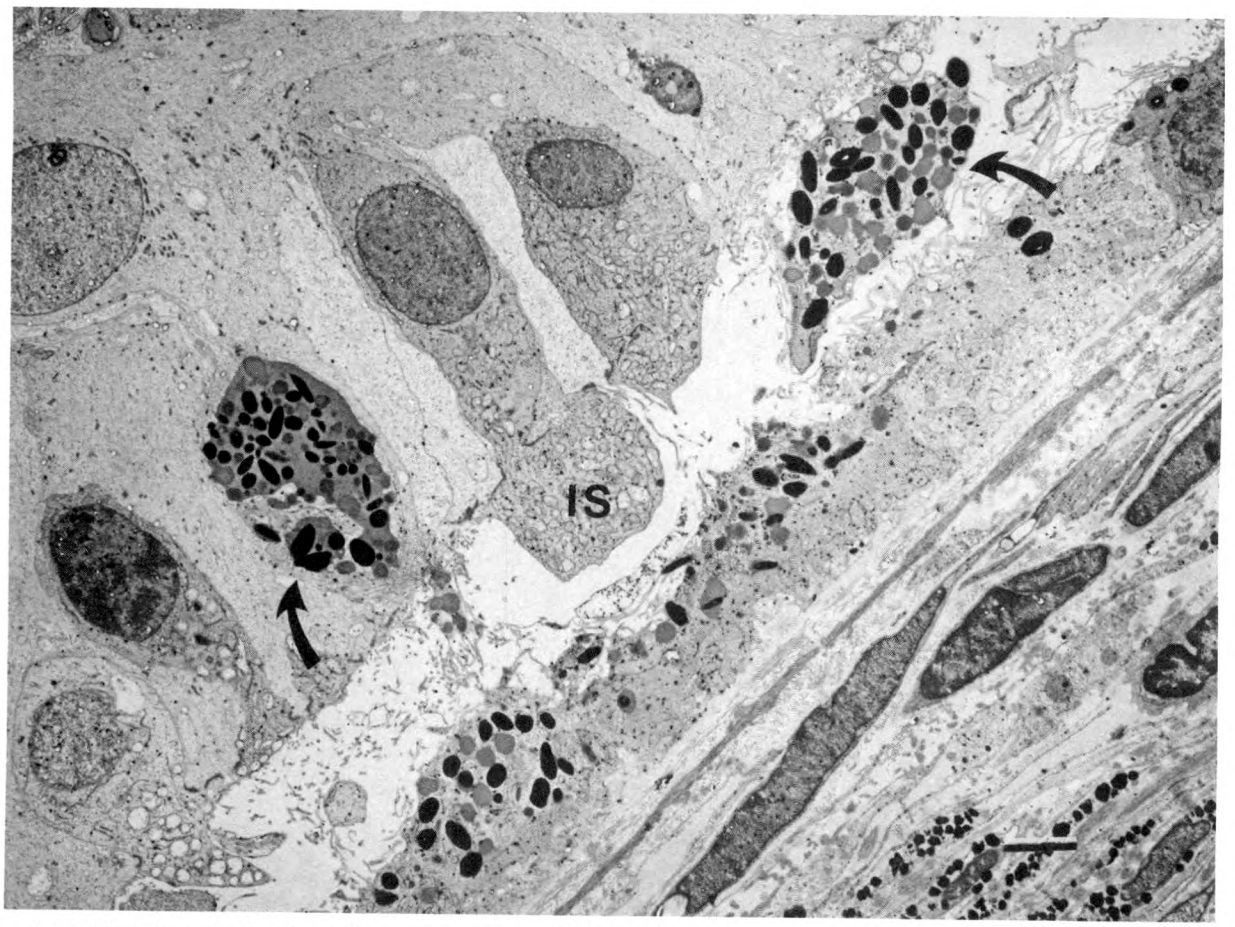


Fig. 7 (Berson and Adamian). Remaining cones with inner segments (IS) abut an irregular pigment epithelium. Curved arrows show intraretinal or subretinal pigment-containing cells (bar = 3 μm).

roid appeared intact. These histologic findings suggest that both the photoreceptors and the pigment epithelium are abnormal in this condition.

This study is consistent with two previous studies of a 56-year-old man and a 45-year-old man with Usher's syndrome type II in which 60% and 80%, respectively, of the axonemes within the photoreceptor connecting cilia had an abnormal configuration of microtubules with either extra microtubules or a disruption of the nexin link between doublet microtubules.[5,6] These findings in Usher's syndrome type II contrast with normal photoreceptor cilia found in other forms of retinitis pigmentosa without deafness.[6] Sperm with extra or missing doublet microtubules with abnormal folding of the tails have been observed in nine patients with Usher's syndrome type II,[5] which was similar to the abnormalities in our autopsy eyes. Abnormal nasal cilia with missing doublet microtubules have also been reported in patients with this syndrome.[7,8]

The mechanism by which the observed structural changes in the connecting cilia could lead to photoreceptor cell death remains to be defined. Abnormalities in the cilia may possibly affect microtubule-membrane crosslinkers[9,10] and the membrane itself, with consequent impairment of the process of outer segment renewal. Actin, a component that appears essential for normal outer segment disk addition in both amphibians and mammals, radiates in bundles of short filaments from between the axonemal microtubule doublets[11]; perhaps if the pattern of microtubule doublets is altered,

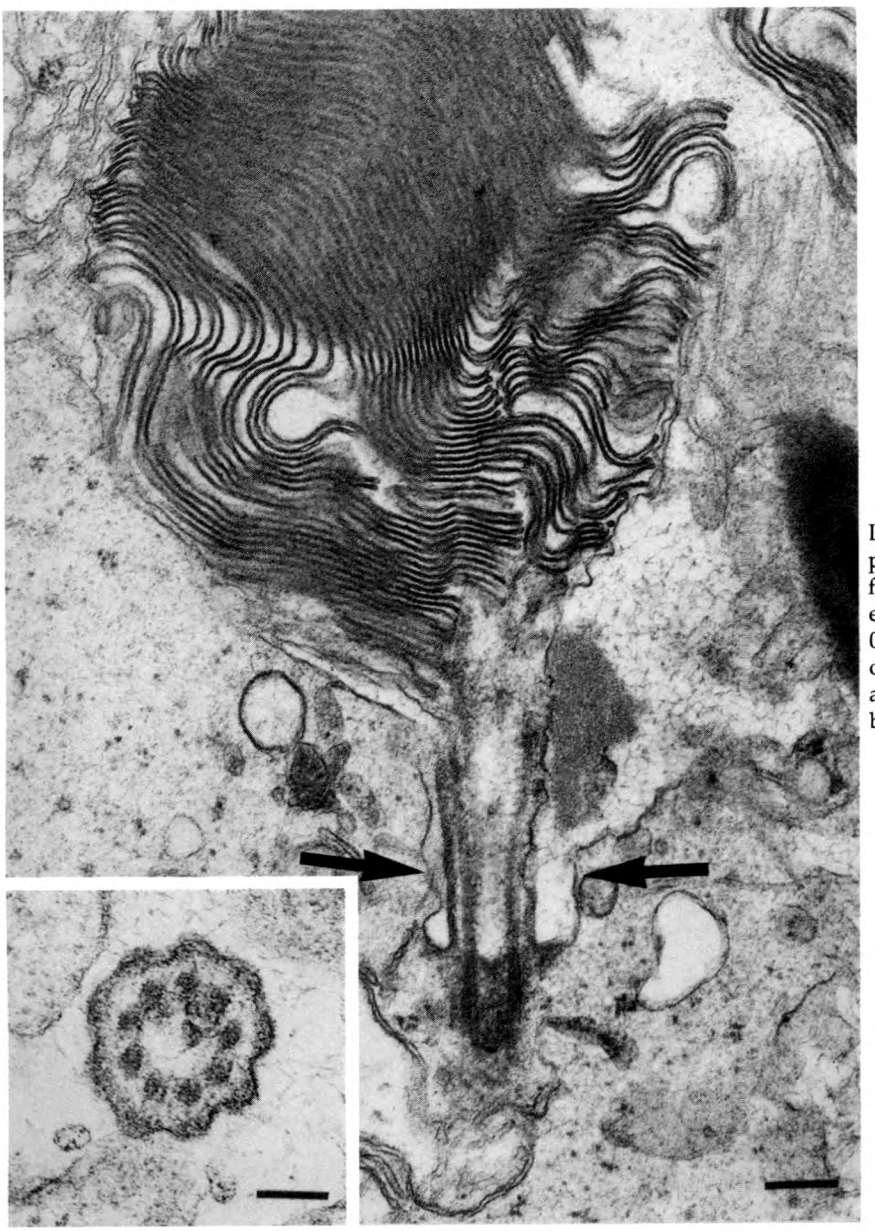


Fig. 8 (Berson and Adamian). Longitudinal section of a rod photoreceptor in the macula from the autopsy eye with Usher's syndrome type II (bar = 0.25 μm). A transverse section of the cilium at the level of the arrows shows extra microtubules (inset, bar = 0.13 μm).

the function of actin is also disrupted, with corresponding disruption of outer segment disk formation. Transport of soluble proteins such as arrestin from the inner to the outer segment may be disrupted because of an abnormality in the structure of the cilia with consequent effects on photoreceptor function and viability.

Gene linkage analyses have shown that Usher's syndrome type II is localized on the long arm of chromosome 1.[12-14] Further molecular genetic studies, focused on genes encoding for structural elements in the cilia, as they are discovered, may help to determine the underlying cause of this condition.



Fig. 9 (Berson and Adamian). Longitudinal section of a rod photoreceptor in the macula of an autopsy control eye from a normal patient (bar = 0.25 μm). A transverse section of the cilium at the level of the arrows shows the normal number of nine doublet microtubules (inset, bar = 0.13 μm) in contrast to the extra microtubules in the eye with Usher's syndrome type II taken at autopsy, seen in Figure 8.

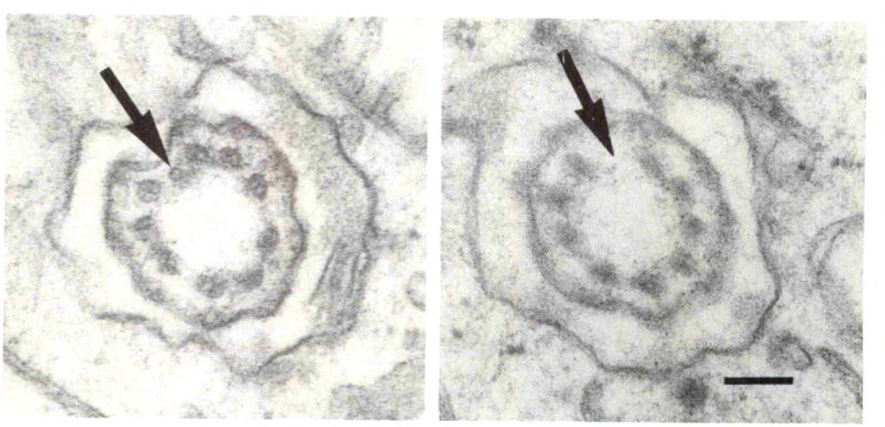


Fig. 10 (Berson and Adamian). Electron micrographs of photoreceptor cilia from the parafovea of the eye with Usher's syndrome type II. Left, An extra singlet microtubule (arrow) is shown. Right, An apparent disruption of the nexin link between microtubules is illustrated (bar = 0.13 μm).

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Visual Field Defects in Patients With Normal-tension Glaucoma and Patients With High-tension Glaucoma

John H. Zeiter, M.D., Dong H. Shin, M.D., Mark S. Juzych, M.D., Tim S. Jarvi, M.D., Thomas C. Spoor, M.D., and Fred Zwas, Ph.D.

We compared the automated visual field test results of 24 patients with normal-tension glaucoma and 24 patients with high-tension glaucoma who were closely matched for the amount of visual field loss to determine any differences in the characteristics of visual field defects between the two groups. Patients were matched with a maximum allowable difference in mean deviation of 0.3 dB. Although the normal-tension group had a greater amount of focal visual field loss (pattern standard deviation), the difference was not statistically significant (P = .628). Additionally, there was no statistically significant difference in the amount of diffuse or focal visual field damage in the superior hemifields between the two groups; however, the patients with normal-tension glaucoma had a significantly greater amount of localized visual field loss in the inferior hemifield than the patients with high-tension glaucoma (P = .015). Our data support the hypothesis that a vascular mechanism may have a greater role in the pathogenesis of optic nerve damage and visual field loss in patients with normal-tension glaucoma than in patients with high-tension glaucoma.

SINCE the initial description of a patient with glaucomatous optic nerve damage and visual field loss in the absence of increased intraocular pressure by Von Graefe[1] in 1857, the relationship between intraocular pressure, optic nerve damage, and visual field loss has aroused controversy. A better understanding of the pathogenesis of high-tension and normal-tension glaucoma might result if one could show differences in the characteristics of optic nerve damage and visual field defects between these two types. Unfortunately, there has been little agreement in published reports as to the similarities and differences of these characteristics in patients with normal-tension glaucoma and patients with high-tension glaucoma.

Some investigators have shown that visual field defects in patients with normal-tension glaucoma as compared to patients with high-tension glaucoma tend to be of sudden onset,[2] closer to fixation,[2-5] deeper and steeper,[2-5] more localized or less diffuse,[6-9] and more common in the superior hemifield.[10,11] However, other investigators have found no differences between the visual field defects in patients with normal-tension glaucoma and patients with high-tension glaucoma.[12-15] The reasons for such controversy appear to be caused by differences in study designs, including different types of perimetry, various definitions of normal-tension glaucoma regarding the highest recorded intraocular pressure, different stages of optic nerve damage and visual field loss, and different methods used in statistical analysis of the data.

We designed a study to compare the visual field defects of patients with normal-tension glaucoma and patients with high-tension glaucoma by using strict criteria for defining normal-tension glaucoma and closely matching both groups with respect to the amount of visual field loss.

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From the Kresge Eye Institute, Wayne State University School of Medicine, Detroit, Michigan. This study was presented in part at the annual meeting of the Association for Research in Vision and Ophthalmology, Sarasota, Florida, May 8, 1992.

Reprint requests to Dong H. Shin, M.D., Kresge Eye Institute, 4717 St. Antoine Blvd., Detroit, MI 48201.

Patients and Methods

We identified 24 patients with normal-tension glaucoma. Each patient had glaucomatous optic nerve damage, open anterior chamber angles on gonioscopy, a maximum recorded

intraocular pressure that did not exceed 22 mm Hg by Goldmann applanation tonometry, a diurnal intraocular pressure curve done without therapy with a minimum of 12 measurements over at least a four-week period, a visual acuity of 20/30 or better, a pupil diameter of at least 3 mm, and a reliable visual field test (fixation losses less than 20% and false-positive and false-negative errors less than 33% according to the manufacturer's criteria [Allergan Humphrey, San Leandro, California]) with reproducible Aulhorn's stage 1, 2, or 3 visual field defects[16] in at least one eye. In stage 1, relative defects are seen in the area of Bjerrum's scotoma. Stage 2 shows deep defects in the area of Bjerrum's scotoma, which form an incomplete arcuate scotoma, not yet connected to the blind spot. In stage 3, the arcuate defect is connected to the blind spot often with breakthrough into the nasal periphery. Cup/disk ratio was determined by examination of the dilated fundus performed by one glaucoma subspecialist by using contour to establish the vertical cup/disk ratio. Fundus examination for the cup/disk ratio determination was binocular by using a slit-lamp biomicroscope and a contact lens, Hruby lens, or a 78-diopter double aspheric lens. When binocular examination was not possible because of a poorly dilatable pupil, however, direct ophthalmoscopy with monocular clues such as disk vessel bending was used for determination of the vertical cup/disk ratio by contour. Patients were excluded if they had a history of trauma or any ocular diseases known to affect the visual field, such as diabetic retinopathy, macular degeneration, or a vascular occlusion. Also, patients with optic neuropathy other than glaucoma, local disk malformations, or neurologic or orbital abnormalities confirmed by computed tomography or serologic studies when applicable were excluded. Patients with advanced visual field loss (mean deviation $\geq$ 20 dB) were also excluded from the study. If a patient had visual field loss in both eyes, then one eye was randomly selected by the toss of a coin.

The 24 Humphrey visual fields from the 24 patients with normal-tension glaucoma were matched closely for extent of visual field damage to 24 Humphrey visual fields of 24 patients with high-tension glaucoma, with a maximum allowable difference in mean deviation of 0.3 dB. The visual fields of patients with high-tension glaucoma were selected from 162 visual field examinations of 62 patients with high-tension glaucoma. All patients included in the high-tension group had primary open-angle glaucoma with intraocular pressures of 26 mm Hg or greater before the initiation of therapy, glaucomatous optic nerve damage, open angles with mild to moderate pigment in the trabecular meshwork on gonioscopy, and reliable Humphrey visual field tests with Aulhorn's stage 1, 2, or 3 visual field defects. Patients with high-tension glaucoma with a visual acuity worse than 20/30, a pupil diameter less than 3 mm, or any other ocular condition known to influence the visual field were excluded. All visual field examinations were performed by trained technicians with a visual field analyzer (Allergan Humphrey 24-2 Threshold Program using Stimulus III, Allergan Humphrey, San Leandro, California).

To determine if there was a difference in the frequency of visual field defects close to fixation between patients with normal-tension glaucoma and patients with high-tension glaucoma, we counted the number of patients in each group with scotomas extending to within 6 degrees of central fixation. Patients were counted if any one of the central four threshold values on the total deviation plot decreased 10 dB or more below age-corrected normal values, or if any of the central four threshold values along with contiguous values decreased 5 dB or more below age-corrected normal values.

Because the normal-tension and high-tension groups of patients were closely matched for loss of overall sensitivity (mean deviation), we were able to determine a difference between the two groups with respect to localized visual field loss by comparing the pattern standard deviation.

We then calculated the mean deviations and pattern standard deviations for the superior and inferior hemifields of all 48 patients. We attempted to find whether the superior or the inferior hemifield had more visual field loss both within each group (normal-tension and high-tension groups, respectively) and between each group (normal-tension vs high-tension groups). First, we compared the mean deviations of the superior to the inferior hemifields to determine any differences in diffuse visual field loss within the normal-tension and high-tension groups, respectively. Then we compared the pattern standard deviations of the superior to the inferior hemifields to determine any differences in focal visual field loss within each of the two groups. Finally, we compared the superior and the inferior hemifields, respectively, of the normal-tension group to those of the high-tension group with respect to both

mean deviation and pattern standard deviation.

We used the Wilcoxon signed rank test to compare mean deviation (matched) between patients with normal-tension glaucoma and patients with high-tension glaucoma. We used chi-square analysis with continuity correction to compare gender, race, number of patients in each group with vascular risk factors, and number of patients in each group with scotomas extending to within 6 degrees of central fixation. The Mann-Whitney U test was used for other unpaired statistical comparisons.

Results

The mean deviations, cup/disk ratios, and other demographic data for the normal-tension and high-tension glaucoma groups were analyzed (Table 1). As expected, the mean deviation values that were matched to within 0.3 dB in the selection process were almost identical in the two groups. As reported by other investigators, the normal-tension group had a younger mean age[2] and a larger mean cup/disk ratio for a given amount of visual field loss[2,8,17] than the high-tension group. However, the differences were not statistically significant (P = .170 and P = .350, respectively). There were no significant differences in the gender, race, or systemic vascular risk factors between the two groups.

We studied the differences in the number of patients with defects extending to within 6 degrees of central fixation, in the amount of localized visual field loss (pattern standard deviation), and in the amounts of generalized and localized visual field loss in the upper and lower hemifields of the normal-tension and high-tension glaucoma groups (Table 2). We found no statistically significant difference in the number of patients with scotomas falling within 6 degrees of central fixation (P = .555). Although the normal-tension glaucoma group had a larger pattern standard deviation than the high-tension glaucoma group overall (7.37 ± 2.94 dB vs 6.94 ± 3.08 dB), this difference was not statistically significant (P = .628).

When comparing the amount of superior to inferior hemifield involvement within the high-tension glaucoma group, there was significantly more involvement of the superior than the inferior hemifield with respect to both mean deviation and pattern standard deviation (P = .004 and P = .0003, respectively). However, in the normal-tension glaucoma group, there was a tendency toward equal involvement of the two hemifields with no significant differences noted in either the mean deviation or the pattern standard deviation (P = .918 and P = .350,

TABLE 1
BACKGROUND VARIABLES FOR NORMAL-TENSION AND HIGH-TENSION GROUPS

VARIABLE	PATIENTS WITH NORMAL-TENSION GLAUCOMA (N=24)	PATIENTS WITH HIGH-TENSION GLAUCOMA (N=24)	P VALUE
Mean deviation (dB)	9.16 ± 3.93	9.11 ± 3.89	.475
Cup/disk ratio	0.80 ± 0.10	0.75 ± 0.15	.350
Age (yrs)	67.5 ± 12.1	71.6 ± 13.0	.170
Gender ratio (male:female)	10:14	9:15	.999
Race ratio (black:white)	14:10	16:8	.766
Vascular risk factors*	9 (38%)	10 (42%)	.999

*Number of patients with cardiovascular disease or hypertension or both, or cardiovascular disease or diabetes mellitus, or both.

TABLE 2
COMPARISON OF MEAN DEVIATION AND PATTERN STANDARD DEVIATION FOR NORMAL-TENSION AND HIGH-TENSION GROUPS

	PATIENTS WITH NORMAL-TENSION GLAUCOMA (N=24)	PATIENTS WITH HIGH-TENSION GLAUCOMA (N=24)	P VALUE
Scotomas within 6 degrees of fixation*	13 (54%)	16 (67%)	.555
Pattern standard deviation (dB)	7.37 ± 2.94	6.94 ± 3.08	.628
Superior mean deviation (dB)	10.16 ± 5.86†	12.58 ± 6.43‡	.180
Inferior mean deviation (dB)	9.55 ± 4.65†	7.52 ± 3.10‡	.167
Superior pattern standard deviation (dB)	7.28 ± 4.77§	9.29 ± 5.88‖	.177
Inferior pattern standard deviation (dB)	6.65 ± 4.25§	4.17 ± 1.86‖	.015

*Number of patients with scotomas extending to within 6 degrees of central fixation.
†P = .918.
‡P = .004.
§P = .350.
‖P = .0003.

respectively). There were no statistically significant differences between the normal-tension and high-tension glaucoma groups when comparing the amount of generalized visual field loss in the superior hemifields or the inferior hemifields (P = .180 and P = .167, respectively). However, there was significantly more focal visual field loss located in the inferior hemifield in the normal-tension group than in the high-tension group (P = .015), although there was no difference between the two groups in the amount of focal visual field loss located in the superior hemifield (P = .177).

Discussion

Normal-tension glaucoma has been described as having typical glaucomatous optic disk changes with resulting visual field loss, open angles, and intraocular pressures within the statistically normal range. Since the initial description of this entity, many questions have been raised concerning the mechanisms of optic nerve damage in glaucoma, and whether there are different mechanisms involved in the pathogenesis of normal-tension vs high-tension glaucoma. For more than a decade, authors have been studying both similarities and differences in the visual field defects between patients with normal-tension glaucoma and patients with high-tension glaucoma.[2-15] A different pattern of visual field loss in these two populations raises the possibility of a different mechanism of optic nerve damage and might suggest a difference in the relative roles that vascular ischemia and intraocular pressure have in the pathogenesis of normal-tension and high-tension glaucoma. Unfortunately, there has been little agreement on what types of differences in visual field loss exist between these two groups of patients.

Some investigators found that visual field defects were close to fixation much more commonly in patients with low-tension glaucoma than patients with high-tension glaucoma and that because of this, patients with low-tension glaucoma lost visual acuity earlier and more frequently than patients with high-tension glaucoma.[2,4] Conversely, many other investigators have found no significant difference in the number of patients with normal-tension glaucoma and patients with high-tension glaucoma with visual field defects near fixation.[11,12,15,18] In our study, unlike the previously mentioned studies, the visual fields were closely matched for the amount of visual field loss in each group, and we found no significant difference in the number of patients with normal-tension glaucoma and patients with high-tension glaucoma with scotomas extending to within 6 degrees of central fixation.

Recently, Chauhan and associates[9] found that individuals with normal-tension glaucoma had greater areas of normal sensitivity and, therefore, more localized visual field defects than individuals with high-tension glaucoma. Previously, two separate studies had shown that patients with glaucoma with generalized visual field loss had a higher mean intraocular pressure than those with more localized visual field loss.[6,7] We investigated these findings by comparing the pattern standard deviation values (localized visual field loss) between normal-tension and high-tension groups that had been closely matched for mean deviation (generalized visual field loss). Although the normal-tension group in our study had a greater amount of localized visual field loss than the high-tension group, this difference was not statistically significant. This finding is similar to that of Paul, Cohn, and Weber,[19] who recently found no significant difference in the pattern standard deviation between patients with low-tension glaucoma (intraocular pressure $\leq$ 21 mm Hg) and patients with high-tension glaucoma (intraocular pressure $\geq$ 28 mm Hg) with similar mean deviations.

We may not have found a significantly greater amount of localized visual field loss in patients with normal-tension glaucoma because the average mean deviation in our patients was higher than that of the patients in previous studies,[6,7,9] which indicates slightly more advanced visual field loss in our groups. As visual field loss becomes more advanced, any differences in the amount of localized and diffuse damage between normal-tension and high-tension groups may become less. Additionally, the maximum intraocular pressure of the normal-tension group and the minimum intraocular pressure of the high-tension group in our study were only 4 mm Hg apart, which may be responsible for some overlap of localized and diffuse damage between the two groups.

In our study, we found a tendency toward equal involvement of the superior and inferior hemifields in the patients with normal-tension glaucoma. However, in the patients with high-

tension glaucoma, the superior hemifield was remarkably more involved than the inferior hemifield with respect to both generalized and localized visual field loss. This finding that patients with early to moderate primary open-angle glaucoma have visual field defects that involve the superior hemifield to a greater extent than the inferior hemifield has been well documented.[20-24]

Additionally, many investigators have addressed the issue of whether there is any difference in the distribution of visual field defects over the superior and inferior hemifields between patients with normal-tension glaucoma and patients with high-tension glaucoma.[5,10-13,18] Although most studies found no differences between the two groups,[10,12,13] Gramer, Althaus and Leydhecker[5] found a preponderance of inferonasal visual field defects in patients with normal-tension glaucoma, whereas Greve and Geijssen[11,18] found greater involvement of the superior hemifield in the normal-tension group as compared to the high-tension group. We found no statistically significant difference in the distribution of generalized visual field loss over the superior and inferior hemifields between the two groups. However, when we focused on localized visual field loss, we found that the normal-tension group had a significantly greater amount of focal visual field defects in the inferior hemifield.

This finding of a preponderance of localized visual field loss in the inferior hemifield of patients with normal-tension glaucoma as compared to patients with high-tension glaucoma may have important implications as to the relative role that vascular ischemia may have in optic nerve damage in patients with normal-tension glaucoma. The most frequent visual field defect in nonarteritic anterior ischemic optic neuropathy is an altitudinal defect involving the inferior hemifield.[13,25,26] Additionally, we have shown in previous studies that patients with primary open-angle glaucoma with diabetes mellitus develop inferior visual field defects more frequently than patients with primary open-angle glaucoma without diabetes mellitus, speculating the possibility of a vascular contribution at the level of the optic nerve head in patients with glaucoma and diabetes.[27,28] Recently, Gramer and Althaus[29] found that patients with primary open-angle glaucoma with low systolic blood pressure had more severe visual field defects in the lower hemifield compared to the upper hemifield. Additionally, they found that the visual field defects in these patients with lower hemifield involvement were twice as likely to deteriorate as those in patients with superior visual field loss.[29]

Several authors have suggested that vascular factors in addition to intraocular pressure have an important role in the pathogenesis of glaucoma.[29-32] Also, there appears to be an association between normal-tension glaucoma and migraine headaches[33] as well as ocular vasospasm,[34,35] which strongly suggests a possible vascular origin in this disease. Our findings of a greater amount of localized visual field loss in the inferior hemifield of patients with normal-tension glaucoma as compared to patients with high-tension glaucoma is one more observation in support of the hypothesis that vascular ischemia may have a larger role in the pathogenesis of optic nerve damage and visual field loss in normal-tension glaucoma than in high-tension glaucoma.

Although we found more patients with normal-tension glaucoma with localized visual field loss in the inferior hemifield, many patients in the high-tension group also had some localized defects in the inferior half of the visual field. This finding reminds us that there is a spectrum of visual field defects involving varying amounts of the inferior and superior hemifields between the two groups. Additionally, when defining the two groups on the basis of intraocular pressure alone, one cannot control for other possible risk factors in the production of glaucoma. Also, even with the use of diurnal pressure curves in defining normal-tension glaucoma, there may still be some overlap of intraocular pressure between the two groups. These unavoidable circumstances along with variations in study designs and different stages of optic nerve damage and visual field loss help explain why there has been little agreement on the differences in visual field defects between patients with normal-tension glaucoma and patients with high-tension glaucoma.

Additional studies using patients closely matched for the amount of visual field loss will help further define differences in visual field defects between patients with normal-tension glaucoma and patients with high-tension glaucoma and provide more insight into the relative roles of intraocular pressure and vascular ischemia in the production of glaucoma.

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LETTERS TO THE JOURNAL

Low-tension Glaucoma in Identical Twins

Steven Ofner, M.D., and John R. Samples, M.D.

Casey Eye Institute, Oregon Health Sciences University.

Inquiries to Steven Ofner, M.D., Eugene Eye Care Associates, P.C., 1415 Pearl St., Eugene, OR 97401.

Congenital glaucoma in identical twins has been observed,[1] as has primary open-angle glaucoma in monozygotic twin pairs,[2] but low-tension glaucoma in identical twins has not been well documented. In a large study of twins with chronic open-angle glaucoma, 29 monozygotic and 79 dizygotic pairs were studied.[3] In another large study of the incidence of ocular disease in twins, low-tension glaucoma was not described.[4] However, intraocular pressure criteria were probably part of the study. An autosomal dominant form of low-tension glaucoma has been previously described.[5] We managed a case of low-tension glaucoma in identical twins.

A 44-year-old woman was referred for examination after routine automated perimetry disclosed an abnormality in the visual field. Her ocular and medical history were noncontributory. Her identical twin sister was also healthy.

Ocular examination showed a visual acuity of 20/20 in both eyes. The left eye had an afferent pupillary defect. There were inferior iris transillumination defects in both eyes without Krukenberg's spindles. Gonioscopy showed the iridocorneal angle to be open 360 degrees to the scleral spur with mild trabecular pigmentation. The optic disk had a cup/disk ratio of 0.7 in both eyes, with a splinter hemorrhage at the disk margin in the superotemporal portion of the left eye. Static threshold perimetry disclosed a dense inferonasal step in the left eye that corresponded with the disk hemorrhage. The visual field in the right eye showed an inferonasal depression of retinal sensitivity.

The highest intraocular pressure measured was 21 mm Hg in both eyes during an all-day diurnal curve study. The lowest intraocular pressures were 16 mm Hg in the right eye and 17 mm Hg in the left eye. Intraocular pressure decreased to 13 mm Hg in the right eye and 15 mm Hg in the left eye while the patient was instilling timolol 0.5% twice a day in both eyes.

Subsequently, the patient's asymptomatic, identical twin sister was examined. Results of her ocular examination were similar to those of her twin sister, except her pupillary responses were normal. No iris transillumination defects were noted. The optic disk showed a cup/disk ratio of 0.7, with some sloping temporally in both eyes. A large splinter hemorrhage was present superotemporally in the right eye, which was contralateral to the eye of her twin sister. Results of static threshold perimetry were normal in the left eye, but showed an inferonasal defect in the right eye.

Results of magnetic resonance imaging of the brain and orbits with gadolinium contrast were within normal limits as were results of a complete physical examination and carotid artery duplex scanning for each twin sister. The highest intraocular pressures measured were 21 mm Hg in the right eye and 19 mm Hg in the left eye during an all-day diurnal curve study. The lowest intraocular pressures were 18 mm Hg in the right eye and 15 mm Hg in the left eye. The

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intraocular pressure decreased to 13 mm Hg in the right eye and 12 mm Hg in the left eye while the patient was instilling timolol 0.5% twice a day in both eyes. Both twins always had a higher intraocular pressure in the eye with the splinter hemorrhage and visual field defect when a difference between the two eyes existed.

Recent results of static threshold perimetry in the parents were normal.

The theories regarding the origin of low-tension glaucoma may be primarily grouped into vascular or structural theories. The occurrence of low-tension glaucoma in identical twins may be evidence for an inherited structural abnormality, perhaps in the collagen of the lamina cribrosa, with secondary axonal dysfunction contributing to the origin of this disease. Our patients are particularly interesting because their fellow eyes were the ones that developed optic disk splinter hemorrhages and visual field defects. Some investigators have suggested that the large size of the optic cups in the normal fellow eyes of patients with unilateral low-tension glaucoma suggests that intraocular pressure increase was not the major reason for their large optic cups. Our patients, likewise, had large cupping in the fellow eye. We suggest this as further evidence for a structural abnormality in the optic nerve, as some investigators have suggested for glaucoma. Other investigators have suggested a vascular origin for this disease. More likely, this is a disease with an origin associated with many factors of varying importance. Our case suggests a congenital structural defect as another factor.

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Impending Macular Hole Associated With Topical Pilocarpine

William L. Benedict, M.D., and Michel Shami, M.D.

Department of Ophthalmology and Visual Sciences, Texas Tech University Health Sciences Center.

Inquiries to Michel J. Shami, M.D., Department of Ophthalmology, Texas Tech University Health Sciences Center, Lubbock, TX 79430.

Rhegmatogenous retinal detachments and peripheral retinal tears have been associated with miotic therapy.[1] We treated a patient who developed a stage I-A macular hole (foveolar detachment) coincident with the initiation of pilocarpine therapy for glaucoma. The impending hole resolved after the pilocarpine was stopped.

The patient was a 69-year-old white woman. Results of her initial macular examination by her referring ophthalmologist were normal. She was noted to have early glaucoma, and pilocarpine 2% in each eye, four times per day was started. One month later the patient returned with complaints of blurred vision in the right eye. Her visual acuity was 20/20 bilaterally. An impending macular hole was noted in the right eye and she was referred to us for further examination.

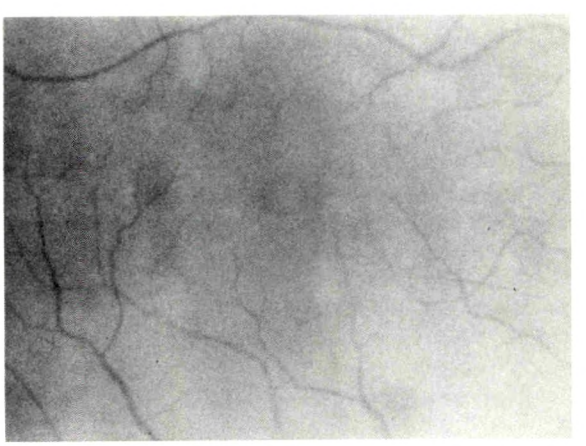


Fig. 1 (Benedict and Shami). Stage I-A macular hole one month after the initiation of topical pilocarpine. Note the absent foveal reflex and the small yellow spot centered in the fovea.

Our examination disclosed narrow chamber angles bilaterally and moderate nuclear sclerotic lens changes. There was loss of the foveal reflex and a small yellow spot located centrally in the fovea of her right eye (Fig. 1). No associated posterior vitreal detachment was found. An epiretinal membrane was present at the surface of the left macula, and both retinas were peripherally unremarkable.

The patient returned seven days later complaining of intermittent halos surrounding lights. Her intraocular pressure was 20 mm Hg bilaterally and gonioscopy disclosed significant peripheral iridocorneal apposition in the right eye. A laser peripheral iridectomy was performed.

Ophthalmoscopy repeated three weeks later (one month after discontinuation of the pilocarpine) disclosed complete resolution of the impending macular hole (Fig. 2). The posterior vitreous was still attached to the macula.

Miotics have been associated with retinal tears, secondary retinal detachments, and macular hole formation.[2] The postulated mechanism is that miotic-induced accommodation, which has been shown to result in an anterior shift of the posterior lens surface,[3] causes anterior displacement of the vitreous. This results in anteroposterior vitreofoveal traction.

Our patient developed a stage I-A macular hole (foveolar detachment) within one month after initiation of pilocarpine for glaucoma. One month after the miotic was stopped, in the absence of a posterior vitreous detachment, the impending hole resolved. The association of the impending hole with the miotic therapy suggests a causal relationship. We believe that miotic-induced forward displacement of the vitreous placed traction on the fovea and caused a small foveal detachment. Removal of the miotic, and the resultant ciliary body relaxation, then relieved the vitreofoveal traction and allowed the retina to settle.

The observation that impending macular holes are usually aborted if a posterior vitreal detachment occurs before the development of a full-thickness hole[4] supports this proposed mechanism for miotic-induced macular hole formation.

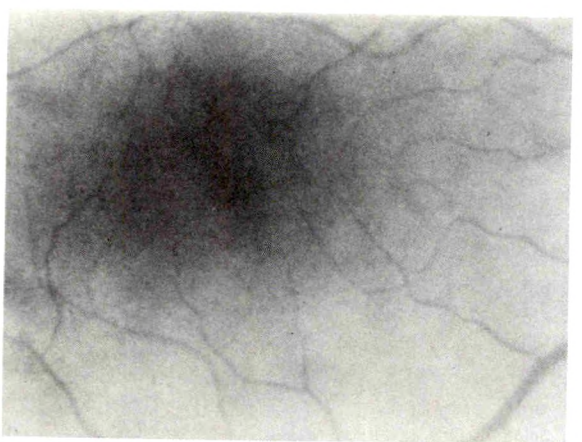


Fig. 2 (Benedict and Shami). Aborted macular hole in the same patient one month after the discontinuation of pilocarpine. Note the resolution of the central yellow spot.

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The Association of Iridoschisis and Angle-recession Glaucoma

John F. Salmon, F.C.Ophth.

Department of Ophthalmology, University of Cape Town and Groote Schuur Hospital.

Inquiries to John F. Salmon, F.C.Ophth., Department of Ophthalmology, Medical School, University of Cape Town, Observatory 7925, Cape Town, South Africa.

The term iridoschisis describes a localized cleavage of the iris into two layers, with subsequent disintegration of the anterior leaf.[1] Iridoschisis has been associated mainly with primary angle-closure glaucoma, but has also been described as an idiopathic iris atrophy of old age.[1-3] In three cases, iridoschisis was reported secondary to ocular trauma and in one case in association with angle recession.[3-5]

Case 1

A 54-year-old man had painful eyes and a history of gradual visual loss. He had had recurrent facial and ocular trauma as a young

man. On examination the visual acuity was R.E.: 20/60 with a −1.25 −1.50 × 90 degree correction and L.E.: 20/100 with a −1.00 −1.00 × 90 degree correction. Corneal edema was present in the right eye. The intraocular pressure was 57 mm Hg in the right eye and 58 mm Hg in the left eye. Advanced glaucomatous disk damage was present in both eyes. He had evidence of superior and inferior localized iridoschisis, with round pupils (Figure). Gonioscopy disclosed 180 degrees of angle recession in the right eye and 90 degrees of angle recession in the left eye. The intraocular pressures were not controlled medically, and a trabeculectomy was performed in both eyes. A Molteno tube was subsequently implanted in the left eye. Four years later, the intraocular pressure has been controlled in both eyes with topical glaucoma medication. No further disk damage has occurred, and the iridoschisis has remained unaltered.

Case 2

A 50-year-old man had a history of gradual visual loss in his only eye. He had had recurrent trauma to both eyes many years before. On examination, the visual acuity in the right eye was 20/40 with a −0.75 −1.25 × 90 degree correction. Phthisis bulbi was present on the left. The intraocular pressure was 40 mm Hg and glaucomatous disk cupping with advanced visual field loss was found. Iridoschisis was noted in the superior and inferior quadrants of the iris and small iris sphincter tears were present. Gonioscopy disclosed 110 degrees of angle recession. The intraocular pressure was not controlled medically and the patient underwent a trabeculectomy. No progression of the disk cupping or change in the iridoschisis have occurred over an 18-month period.

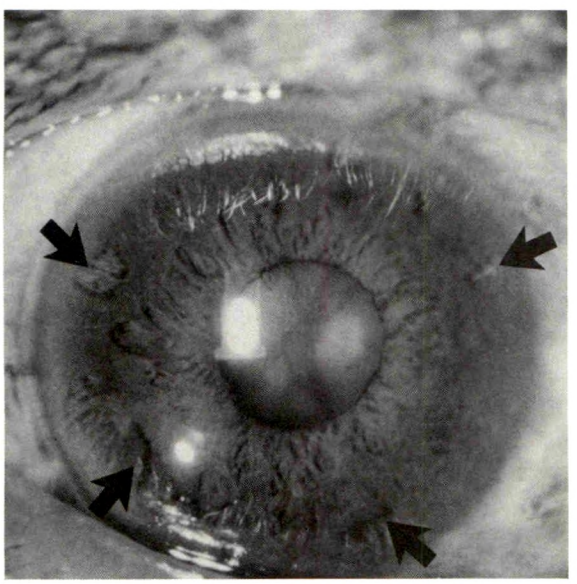


Figure (Salmon). Case 1. Arrows indicate localized areas of iridoschisis involving the superior and inferior quadrants of the iris.

In primary angle-closure glaucoma broad areas of mainly inferior iridoschisis are found, whereas in angle-recession glaucoma the changes are more patchy and involve the superior and inferior quadrants. Although the pathogenesis of iridoschisis in angle-recession glaucoma is unknown, the presence of these iris changes should alert the clinician to the possibility of previous blunt ocular trauma. These cases once again highlight the importance of gonioscopy in patients with iridoschisis.[2]

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Vitreous Pulsations, Relative Hypotony, and Retrobulbar Cyst Associated With a Congenital Optic Pit

Thomas R. Friberg, M.D., and Thomas G. McLellan, M.D.

Department of Ophthalmology, University of Pittsburgh.

Inquiries to Thomas R. Friberg, M.D., The Eye and Ear Institute, 203 Lothrop St., Suite 824, Pittsburgh, PA 15213.

Optic pits develop during embryogenesis when defects in the cribriform plate cause neural tissue to invaginate inward, creating a deep recess within the nerve head. These congenital abnormalities are often associated with overly-

ing fibroglial membranes and serous retinal detachments involving the macula.[1] We examined a patient with an optic pit who had vitreous and glial debris located in the vitreous cavity just anterior to the nerve head. This debris freely pulsated into and out of the pit during the patient's cardiac cycle.

A 61-year-old woman had floaters in her right eye. She had a history of mild amblyopia in the left eye from strabismus, and mild myasthenia gravis for 12 years.

At initial examination, visual acuity was R.E.: 20/20 and L.E.: 20/30. Applanation pressures were 18 mm Hg in the right eye and 12 mm Hg in the left eye. On biomicroscopy, posterior vitreous detachments were visible in both eyes. In the left eye, a deep, gray optic pit was present in the temporal portion of the nerve head. A few hypopigmented streaks in the retinal pigment epithelium radiated from the disk. Glial debris was affixed to the detached posterior hyaloid face and, intermittently, the debris appeared to be sucked into the pit, where it pulsated inward and outward as it gradually disappeared (Fig. 1). These pulsations were synchronous with the patient's heart beat. With ocular movement the glial material was dislodged from the pit and the process would repeat itself. We documented these unusual findings with a scanning laser ophthalmoscope on videotape.

The disparity between the intraocular pressures in her eyes was a consistent finding noted on all three previous ocular examinations. The left eye had the lower pressure by 4 to 9 mm Hg.

At re-examination one year later, the intraocular pressure measured 19 mm Hg in the right eye and 12 mm Hg in the left eye. Gonioscopy showed open and symmetric anterior chamber angles in both eyes. During a Valsalva maneuver, pressures increased 3 mm Hg in both eyes; the debris could be forced into the optic pit by applying digital pressure.

The results of tonography were 0.15 μl/min/mm Hg in the right eye and 0.24 μl/min/mm Hg in the left. B scan ultrasonography disclosed a cystic structure located behind the globe, which communicated with the vitreous cavity through the optic pit (Fig. 2).

Congenital optic pits or atypical colobomas are located within the substance of the nerve head and characteristically have steep walls and are gray in color. Temporally located pits are often associated with serous macular detachments. Proposed sources of the fluid beneath such detachments include cerebrospinal fluid entering the subretinal space through the pit, movement of fluid from the vitreous cavity

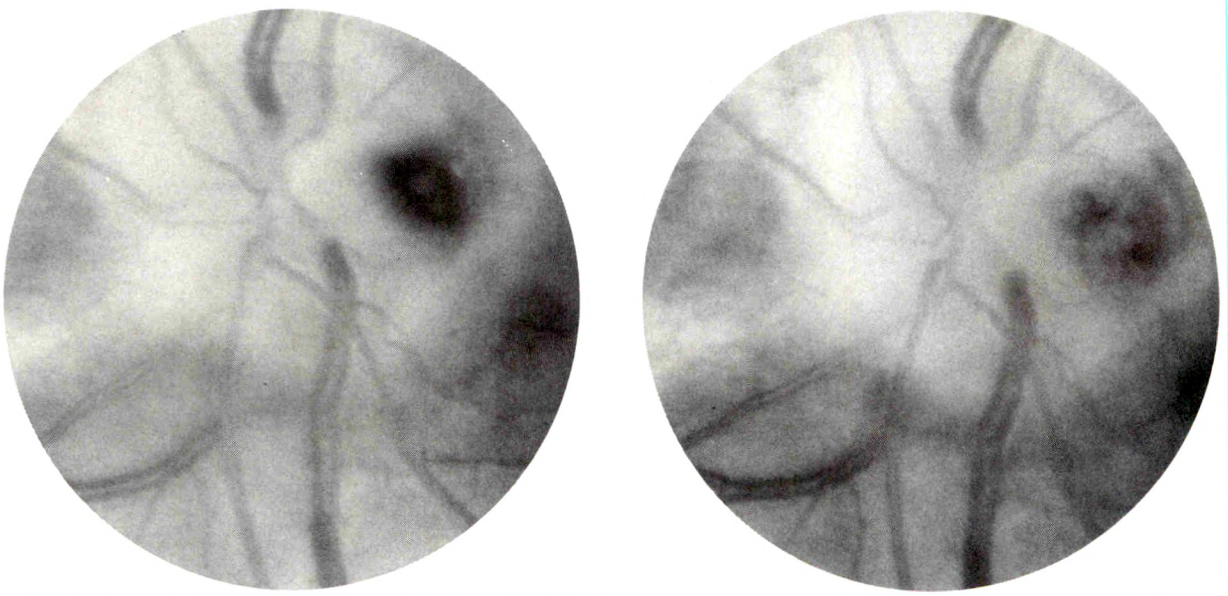


Fig. 1 (Friberg and McLellan). Left, An optic pit is clearly seen in the temporal margin of the nerve head. Deep within the pit, some debris can be seen. Right, The debris has been expelled from the pit and the pit is almost hidden from view. With scanning laser videography, the material was clearly seen to pulsate into and out of the orifice and would intermittently come to rest well within the vitreous cavity.

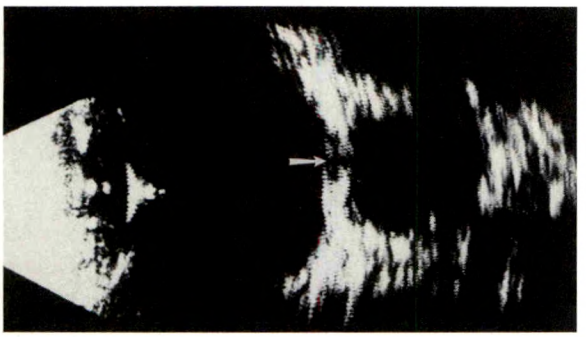


Fig. 2 (Friberg and McLellan). A B-scan ultrasonogram shows a cystic structure behind the globe. The optic pit and the vitreous cavity communicate via the cyst (arrow).

beneath the retina at the pit, leakage from choroidal vessels, and mechanical factors.[1]

True colobomas of the nerve head often exhibit concentric pigment abnormalities along the inferior margin of the disk, which may be tilted. The morning glory syndrome denotes a specific type of coloboma where annular pigmentary changes surround an enlarged, poorly defined, often excavated nerve head.[1-4] A nonrhegmatogenous retinal detachment may be present.

Pulsations of glial tissue within optic pits has been observed and attributed to the motion of surrounding vessels.[1] Contractile movement of the optic nerve itself has been described in the morning glory disk anomaly.[2] In our case, however, vitreous remnants overlying the pit underwent gross displacement into and out of the pit, which communicated with a cyst located within the optic nerve.

The cerebrospinal fluid pressure at the level of the optic nerve is about 2 mm Hg when an individual is seated. We believe the consistently lower intraocular pressure on the side of the pit in our patient was secondary to drainage of intraocular fluid posteriorly through the pit, into the cyst, and ultimately into the subarachnoid space. From our observations, the gross movement of the debris was clearly from the vitreous cavity into the pit. Supporting this assumption was the much higher outflow facility in the patient's left eye. Communications between the vitreous cavity and subarachnoid space and between the subretinal space and subarachnoid space have been demonstrated in patients with the morning glory syndrome.[3,4]

To determine whether eyes with unilateral optic pits tended to have lower intraocular pressures than fellow eyes, we reviewed the charts of all patients with optic pits; ten patients were identified. There was, however, no significant statistical difference between the intraocular pressures in their eyes.

Although our case appears unique, we suggest that other patients with optic pits may harbor unsuspected anomalies such as the cyst within the optic nerve that we found on ultrasonography. Similar cysts have been reported in conjunction with other optic nerve anomalies.[5]

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Spontaneous Retinal Reattachment in a Patient With Persistent Hyperplastic Primary Vitreous and an Optic Nerve Coloboma

Michel Shami, M.D., David McCartney, M.D., William Benedict, M.D., and Charles Barnes, M.D.

Department of Ophthalmology and Visual Sciences, Texas Tech University Health Sciences Center.

Inquiries to Michel J. Shami, M.D., Department of Ophthalmology and Visual Sciences, Texas Tech University Health Sciences Center, Lubbock, TX 79430.

Retinal reattachment seldom occurs without specific reattachment procedures; however, we observed spontaneous reattachment of a traction retinal detachment secondary to persistent

hyperplastic primary vitreous after lensectomy and anterior vitrectomy.

We examined a 6-month-old boy, the product of a normal full-term pregnancy and vaginal delivery, who had a right microphthalmic eye with esotropia. Initial examination disclosed a microphthalmic globe. We measured 40 prism diopters of right esotropia by Krimsky. Corneal diameters were 9 mm vertically and 10 mm horizontally. The anterior chamber was extremely shallow and the iris examination disclosed synechiae to the anterior lens capsule. The lens was densely cataractous, and the pupil dilated poorly. Ophthalmoscopy disclosed an absent red reflex with no view to the posterior pole. A B-scan ultrasound suggested the presence of a funnel-shaped retinal detachment (Fig. 1). The left eye was unremarkable.

We diagnosed persistent hyperplastic primary vitreous, and one week later performed a lensectomy in an attempt to deepen the anterior chamber and preserve the eye. The lensectomy was performed through a limbal approach by using a 23-gauge butterfly needle to form an infusion port and the vitreous cutter. We freed an iridocorneal adhesion and performed a sector iridectomy, because of the dense synechiae encountered between the iris and the anterior lens capsule, allowing us to see easily the ciliary processes. After removal of the lens and retrolenticular membrane, ophthalmoscopy disclosed an open funnel-shaped retinal detachment and a fibrovascular stalk of tissue extending from the central portion of the posterior pole. The optic nerve head was not visible.

Four weeks later ophthalmoscopy disclosed a spontaneous reattachment of the superior retina, though a retinal detachment was still present inferiorly extending from the 4 o'clock to the 8 o'clock meridian. A fibrovascular stalk could still be seen. The optic nerve head, adequately visible, showed a morning glory abnormality (Fig. 2). One, three, and ten months postoperatively ophthalmoscopy disclosed a flat retina. The optic nerve head remained unchanged. The patient's father had an iris coloboma in the right eye and a small choroidal coloboma. Other relatives were unavailable for examination.

Retinal detachment occurs in up to 56% of patients with persistent hyperplastic primary vitreous[1] and is usually secondary to traction caused by preretinal glial strands or to incorporation of peripheral retina in the retrolental membrane with resultant traction. In the presence of an optic nerve coloboma with the morning glory configuration, most physicians attribute retinal detachment to traction caused by abnormal glial tissue within the lesion.[2] In this case, a retrolental membrane was present but there was no abnormal incorporation of the peripheral retina, suggesting the detachment was probably related to anteroposterior traction, which was relieved by the lensectomy-membranectomy, thus allowing spontaneous reattachment of the retina.

Spontaneous reattachment of the retina without surgical intervention was recently described in an infant with microphthalmia associated with a colobomatous nerve and an optic nerve pit,[3] and reattachment of the retina with

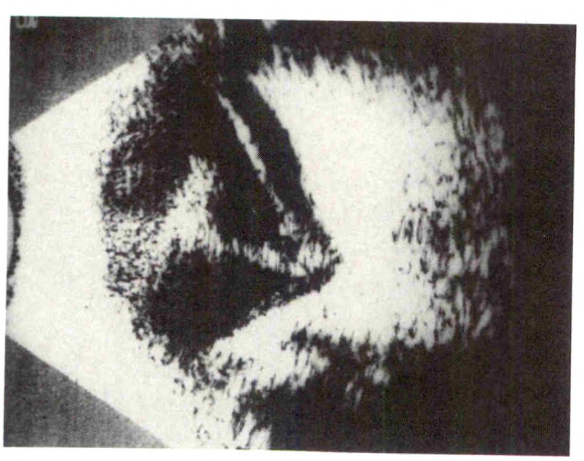


Fig. 1 (Shami and associates). B-scan ultrasound of eye with persistent hyperplastic primary vitreous. Note the funnel-shaped retinal detachment.

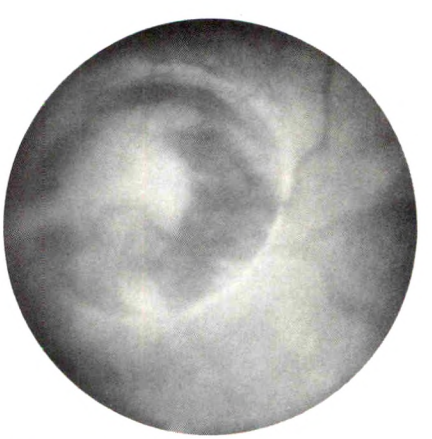


Fig. 2 (Shami and associates). Morning glory anomaly and flat retina noted four months after lensectomy and anterior membranectomy in an eye with persistent hyperplastic primary vitreous.

preservation of some visual acuity was also described in an infant with total retinal attachment (stage 5 retinopathy of prematurity).[4] Our experience with this case of retinal reattachment leads us to suggest cautiously surgical correction of anterior segment abnormality in other similar cases before a more specific retinal reattachment procedure.

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Late-onset Sterile Endophthalmitis After Molteno Tube Implantation

Katrinka L. Heher, M.D., Jennifer I. Lim, M.D., Julia A. Haller, M.D., and Henry D. Jampel, M.D.

Wilmer Ophthalmological Institute, Johns Hopkins University (K.L.H., J.A.H., H.D.J.), and Department of Ophthalmology, Emory University (J.I.L.).

Inquiries to Henry D. Jampel, M.D., Maumenee B-110, Johns Hopkins Hospital, Baltimore, MD 21287-9205.

As tube implant operations become more common, new complications are being recognized.[1] We encountered two cases of sterile endophthalmitis that developed three months after implant operations.

A 21-year-old man who had aniridia, aphakia, and intractable glaucoma underwent single-plate Molteno implantation in his left eye. A 3-0 polypropylene suture was placed in the lumen of the tube at the time of the operation to prevent postoperative hypotony. Nevertheless, the patient developed hypotony and choroidal detachments that required intracameral injection of hyaluronic acid; the removal of the internal occluding suture was thus delayed for 40 days. After the removal of the suture the eye was treated with prednisolone acetate 1%, four times a day, tapered over the next month. Forty-one days after discontinuing topical corticosteroids, the patient developed a painful left eye. The visual acuity was 5/200 (the patient's baseline) and the intraocular pressure was 21 mm Hg. Slit-lamp examination disclosed severe hyperemia, and large cellular aggregates were present throughout the intraocular cavity. Intraocular fluid cultures were obtained through a limbal paracentesis site, and a regimen of prednisolone acetate 1%, every three hours, was begun in the left eye. One week later results of examination were unchanged, and the cultures were repeated. No fungus or bacteria grew out of either set of cultures. Results of a complete blood cell count, HLA-B27, rapid plasma reagin, and chest x-ray were normal.

The patient's pain continued and the cellular aggregates persisted, so the Molteno implant was removed. Four days postoperatively the patient's pain subsided and the cellular clumps were replaced by a severe fine cellular reaction. The topical corticosteroids were tapered over the next month, and all inflammation resolved. Cultures of the implant were negative.

A 75-year-old woman who had diabetes mellitus, pseudophakia, and neovascular glaucoma underwent placement of a single-plate Molteno

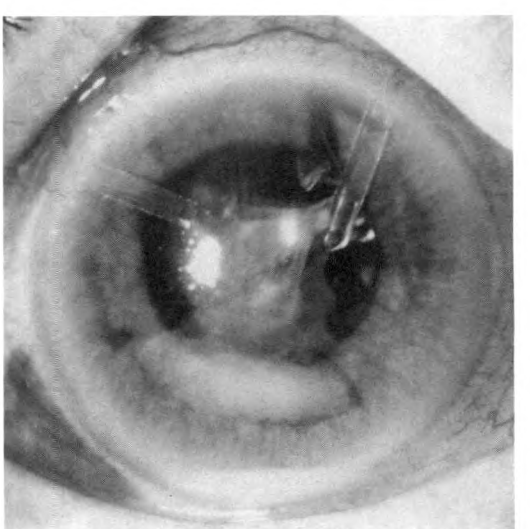


Fig. 1 (Heher and associates). Reduction of layered hypopyon and retraction of fibrin plaque two days after treatment with prednisolone acetate 1% every two hours.

implant in the superotemporal quadrant in the right eye. A 4-0 chromic suture was used to occlude the Molteno tube. On postoperative day 16 the occluding suture was pulled; however, the intraocular pressure remained high at 55 mm Hg on maximal medical therapy.

The patient underwent repeat single-plate Molteno implantation in the superonasal quadrant. Postoperatively a regimen of prednisolone acetate 1%, every two hours, was initiated. After two weeks the topical corticosteroids were decreased to four times a day, and at ten weeks they were tapered and discontinued. One month later the patient was seen because of a two-day history of painless tearing in the right eye. Examination disclosed a visualacuity of 20/100 (the patient's baseline), an intraocular pressure of 14 mm Hg, moderate hyperemia, a 2-mm layered hypopyon, and a fibrin plaque encasing the two Molteno tubes. Vitreous cells were not present. Aqueous fluid cultures were obtained, and the patient was given prednisolone acetate 1% every two hours. After two days the hypopyon had decreased to 0.5 mm and the fibrin clot had retracted (Fig. 1). When the patient returned in two weeks the anterior chamber was uninflamed (Fig. 2), and topical corticosteroids were tapered off. The cultures were negative for fungus and bacteria.

Ball, Loftfield, and Scharfenberg[2] reported seven cases of sterile hypopyons that occurred immediately after the rip-cord removal of the internal occluding suture.[2] They attributed this phenomenon to inflammation induced by the 4-0 chromic suture. The inflammation seen in our patients cannot be explained by this mechanism for two reasons: first, we used a polypropylene occluding suture in the first patient; and second, the inflammatory response in both of our patients occurred months after suture removal.

Although the clinical situation we described is not suggestive of infectious endophthalmitis, ocular cultures are probably mandatory to rule out an infectious cause. After obtaining cultures, frequent topical corticosteroids can be instituted. Topical corticosteroids alone may be sufficient to achieve full resolution of the inflammation; however, implant removal may be required.

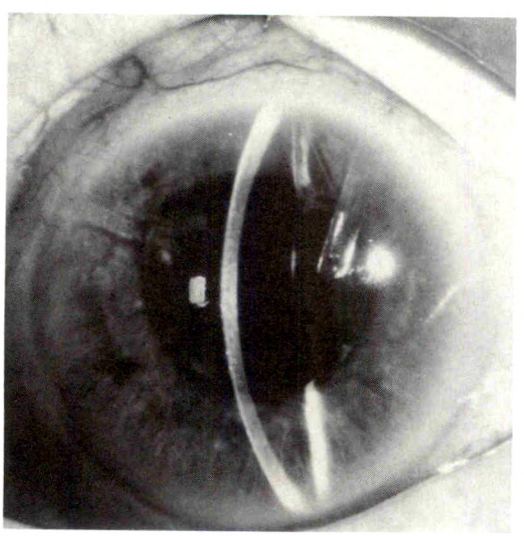


Fig. 2 (Heher and associates). Complete resolution of inflammation after two weeks of topical corticosteroid therapy.

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Xanthomonas maltophilia Endophthalmitis After Implantation of Sustained-release Ganciclovir

Sanford Chen, M.D., Edward M. Stroh, M.D., Kenneth Wald, M.D., and Alex Jalkh, M.D.

Retina Associates, Schepens Eye Research Institute, Massachusetts Eye and Ear Infirmary, Harvard Medical School.

Inquiries to Sanford Chen, M.D., 100 Charles River Plaza, Boston, MA 02114.

Cytomegalovirus retinitis is the most common opportunistic ocular infection in patients with acquired immunodeficiency syndrome (AIDS). It develops in approximately 25% of patients. Untreated, cytomegalovirus retinitis usually spreads progressively and causes retinal necrosis and atrophy.[1]

Current therapy of cytomegalovirus retinitis includes two virustatic drugs, ganciclovir and foscarnet, which are administered through indwelling catheters.[1] For patients intolerant to systemic therapy, ganciclovir can be administered intravitreally. The half-life of ganciclovir

is 13 hours, requiring injections one to three times per week. To avoid complications of multiple intravitreal injections, an implantable sustained-release ganciclovir pellet has been developed.[1] In the phase I trial report, no patient developed endophthalmitis.[2] We managed a case of *Xanthomonas maltophilia* endophthalmitis that developed after implantation of this device.

Xanthomonas maltophilia is an opportunistic, gram-negative species of rod bacteria that is closely related to the *Pseudomonas* species. *Xanthomonas maltophilia* exhibits resistance to many drugs, including all aminoglycosides, quinolones, and most beta-lactam antibiotics. Many infections develop in patients with neutropenia and patients with indwelling catheters.[3,4] Patients with AIDS commonly have neutropenia and indwelling catheters.

Our patient was a 41-year-old man who had had AIDS for two years and who developed cytomegalovirus retinitis in the right eye. He received intravenous ganciclovir through a Hickman catheter, but his treatment was switched to intravitreal ganciclovir after neutropenia developed and intravenous access was lost. After 18 intravitreal injections over a four-month period, he elected to undergo intraocular implantation of a sustained-release ganciclovir pellet. The procedure was uncomplicated. On follow-up examination, there was remission of the retinitis in the right eye; however, the patient had developed cytomegalovirus retinitis in the left eye, and thus underwent similar ganciclovir implantation in that eye. On postoperative day 7, the patient had decreased visual acuity, marked panuveitis, and hypopyon. He was also neutropenic (white blood cell count, 2,500 cells/mm^3; normal, 4,000 to 11,000 cells/mm^3). A vitrectomy was performed with intravitreal injection of vancomycin (1 mg/0.1 ml) and amikacin (0.4 mg/0.1 ml). Adjunctive intravenous vancomycin and tobramycin were also administered. Because there was little vitreitis around the implant, the implant was not removed. Over the next four days, he developed worsening inflammation and initial vitreous cultures identified *Pseudomonas* organisms. A second vitrectomy with removal of the implant and intravitreal injections of amikacin (0.4 mg/0.1 ml) and ciprofloxacin (0.2 mg/0.1 ml) was performed. Two days later, the organism was identified as X. *maltophilia*, sensitive only to ceftazidime and trimethoprim-sulfamethoxazole, and resistant to all aminoglycosides, quinolones, and other beta-lactam antibiotics. Additionally, cultures of the explanted ganciclovir device also grew X. *maltophilia*. Blood, eyelid, and conjunctival cultures were all negative. Intravitreal (1 mg/0.1 ml) and intravenous (1 g/day) ceftazidime therapy was instituted. There was a rapid initial response and a gradual resolution of the panophthalmitis over the course of two weeks. The retinitis in the fellow eye remained well controlled and in complete remission at six months of follow-up.

Intravitreal ganciclovir implants are a promising therapy for some cases of AIDS-associated cytomegalovirus retinitis. The efficacy and complications of this therapy are undergoing evaluation.

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Bilateral Panuveitis, Sebopsoriasis, and Secondary Syphilis in a Patient with Acquired Immunodeficiency Syndrome

Sasikala Pillai, M.D., and Francis DiPaolo, M.D.

District of Columbia General Hospital, Georgetown University Medical Center.

Inquiries to Sasikala Pillai, M.D., District of Columbia General Hospital, Ophthalmology Service, 1900 Massachusetts Ave. S.E., Washington, DC 20003.

We treated a patient with acquired immunodeficiency syndrome (AIDS) who had acute



Fig. 1 (Pillai and DiPaolo). Hyperpigmented scaly plaques of the palms.

bilateral panuveitis, sebopsoriasis, and secondary syphilis.

A 40-year-old man, who was seropositive for human immunodeficiency virus (HIV), had lacrimation, photophobia, and diminished vision in both eyes for three days. At initial examination, he had scaly, hyperkeratotic, pigmented plaques involving the scrotum, perianal area, forearms, soles, palms, and extensor areas of the lower legs (Figs. 1 and 2). Visual acuity was light perception in both eyes and notable findings included bilateral seborrheic blepharitis, fine keratic precipitates with 4+ cells (an intense inflammatory response) and flare in the anterior chamber, posterior synechiae for nearly 360 degrees, and severe vitreitis. Dermatologic diagnosis was sebopsoriasis of the scalp, face, and body, and secondary syphilis of the palms and soles. Laboratory examination disclosed a reactive rapid plasma reagin titer of 1:512 and a reactive fluorescent treponemal antibody-absorption test. Cerebrospinal fluid examination showed a reactive rapid plasma reagin titer of 1:1, and a reactive fluorescent treponemal antibody-absorption test. The test for HLA-B27 was negative. The purified protein derivative test was nonreactive and thoracic radiography disclosed no abnormalities. A skin biopsy of the extensor surface of the leg done to exclude psoriasis disclosed chronic eczema. Treatment with topical corticosteroids and cycloplegics was started. The patient received intravenous aqueous penicillin, 4 million units every four hours for 14 days and oral zidovudine, 100 mg, five times a day. The patient's visual acuity gradually improved to 20/50 in both eyes. The fundi were normal except for mild vitreitis. The skin lesions also improved.



Fig. 2 (Pillai and DiPaolo). Hyperpigmented scaly plaques of the legs.

Seborrheic dermatitis, secondary syphilis, and psoriasis may all have ocular manifestations. Seborrhea is one of the most common cutaneous manifestations of AIDS[1] and may be associated with blepharitis. Psoriasis develops in 1.3% to 2% of HIV-positive patients.[2,3] Syphilis and psoriasis may manifest as iritis and chorioretinitis.[4,5] Psoriasis was excluded on the basis of clinical findings and skin biopsy in our patient. The panuveitis responded to systemic penicillin therapy and topical corticosteroid and cycloplegic drops.

Our patient had an interesting combination of dermatologic and ophthalmic diseases: seborrhea (sebopsoriasis) with blepharitis and secondary syphilis with panuveitis. The prevalence of dermatologic problems associated with ocular manifestations in patients with HIV infections makes it imperative for ophthalmologists to be familiar with these conditions. Proper diagnosis and treatment can cure the condition.

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Bilateral Radiant Damage to the Cornea and Retina After Exposure to a 700-V Electric Discharge

Kip Dolphin, M.D., and Harvey Lincoff, M.D.

New York Hospital-Cornell University Medical Center.

Inquiries to Harvey Lincoff, M.D., New York Hospital, 525 E. 68th St., New York, NY 10021.

Radiant damage to ocular tissues occurs through the following: (1) direct thermal energy, (2) thermoacoustic energy that converts sonic transients to induce thermal injury, and (3) photochemical energy that generates oxygen free radicals and other electronegative species that injure viable tissue.[1,2] We examined a patient who sustained ocular damage by photochemical energy from exposure to a high-voltage electric discharge.

A 26-year-old man, a railroad worker, inadvertently engaged a third rail, which was carrying 700 V of electricity, while attempting to position a steel rail. He tried to avert his eyes, but nevertheless saw an electric arc when the two rails met, which he described as blue and blinding.

Within an hour after the accident, the patient had decreased vision and a blue-dot-like scoto-

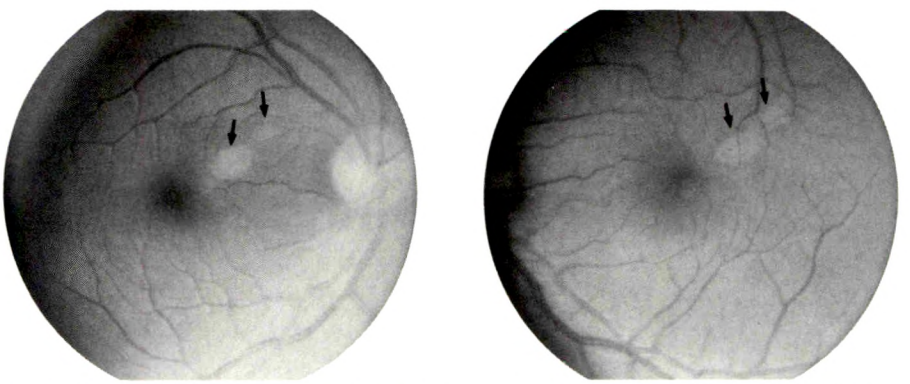


Fig. 1 (Dolphin and Lincoff). The posterior pole of both eyes four hours after exposure to a high-energy electric flash. There are homonymous oval areas of edema in the external layers of the retina (arrows).

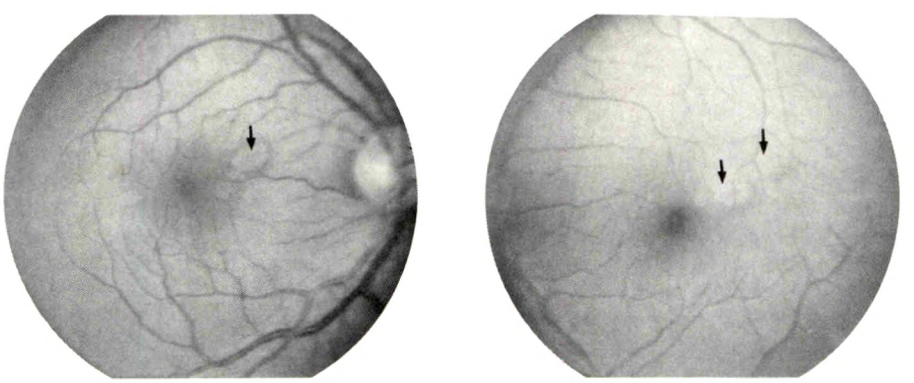


Fig. 2 (Dolphin and Lincoff). The posterior pole of both eyes Four months after exposure to electric flash. Left, The lesions in the right eye have matured, becoming glial opacities in the outer retina (arrow). Right, The smaller lesion in the left eye was no longer apparent (arrows).

ma in the right lower visual field of both eyes when he was examined in an emergency room. He said he had been blinded by the discharge, but that his vision had returned at a reduced level after five minutes. He was photophobic and had increased lacrimation. He was not wearing corrective lenses or protective eyewear at the time of the accident.

The examination disclosed a diminished visual acuity of R.E.: 20/50 and L.E.: 20/30. The pupils were round and reactive.

Both corneas had a broad band of microcystic edema in the interpalpebral zone. The right cornea was more severely affected than the left cornea. The electricity had discharged on the patient's right side. His eyelashes, eyelids, and facial skin were unaffected. Ophthalmoscopy disclosed homonymous juxtafoveal oval white lesions that, on biomicroscopy, appeared to be in the outer layers of the retina. The larger lesions measured 500 × 300 μm in diameter; the smaller lesions were 200 × 100 μm in diameter. In the right eye, the lesions were supranasal to the fovea; in the left eye, they were supratemporal to the fovea (Fig. 1). Perimetry demonstrated homonymous dense scotomas that corresponded to the retinal lesions.

The corneal edema resolved in one week and visual acuity improved to 20/20 in each eye. The paracentral scotomas diminished in density over a four-month period. Mild homonymous scotomas persisted that corresponded to gray proliferative opacities in the outer retinas (Fig. 2). There were no perceptible pigment epithelial changes, which together with the absence of skin burns, suggest the injury that resulted from the high-voltage electric arc, in close proximity, was caused by photochemical energy.

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Parabulbar Anesthesia

Scott Greenbaum, M.D.

Manhattan Eye, Ear, and Throat Hospital.

Inquiries to Scott Greenbaum, M.D., 104-40 Queens Blvd., Forest Hills, NY 11375.

In the natural progression of anterior local anesthetic blocks,[1-3] I have developed a new technique that completely eliminates the needle-inherent risks of glob penetration, optic nerve trauma, and retrobulbar hemorrhage. By using blunt scissors and topical anesthetic, I fashion a buttonhole through the conjunctiva and Tenon's capsule in the inferior temporal or nasal quadrants. A flexible, curved cannula is then passed through the buttonhole and slid under direct observation 3 to 5 mm along the globe. Two milliliters of 4% lidocaine and 0.75% bupivacaine in a 50:50 mixture, without enzyme, is then infused (the reduced amount of anesthetic and the elimination of a diffusing agent make this technique more cost efficient than the standard retrobulbar technique). Immediate anesthesia is achieved, and akinesia has been observed within one minute of administration. In a pilot study, 48 cataract extractions and two pars plana vitrectomies have been performed successfully with no additional anesthetic. A randomized prospective trial comparing the traditional local anesthetic technique with the new parabulbar technique is currently underway at Manhattan Eye, Ear, and Throat Hospital. It appears that effective local anesthesia and akinesia may be achieved without the use of a sharp needle.

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Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Causes and Prognosis in 4,278 Cases of Paralysis of the Oculomotor, Trochlear, and Abducens Cranial Nerves

EDITOR:

In the article, "Causes and prognosis in 4,278 cases of paralysis of the oculomotor, trochlear, and abducens cranial nerves," by B. W. Richards, F. R. Jones, Jr., and B. R. Younge (Am. J. Ophthalmol. 113:489, May 1992), the authors provided data on 1,278 new patients who had oculomotor palsies, and compared their results with results in 3,000 earlier patients, published in the studies of Rucker[1,2] and Rush and Younge.[3] Using patient contact methods developed in the third study to identify false undetermined initial diagnoses and to discover patient recovery, they added useful conclusions concerning the development and outlook of palsies, especially in patients younger than 50 years of age.

I recently reviewed personal cumulative experience of 227 patients who had involvement of the trochlear and abducens cranial nerves, and who were seen in an ambulatory neuro-ophthalmologic private practice that consists mainly of older individuals.

Among 119 patients who had trochlear cranial nerve palsy, the average age was 61.5 years. Vascular causes, including stroke, hypertension, and diabetes, accounted for 39 of the 119, the largest group in this series, and a number that exceeds the vascular as well as undetermined categories of Richards, Jones, and Younge. This unsurprising finding doubtless results from the greater number of older individuals in Florida, compared with Minnesota. (The average age in the recent Mayo Clinic study was not given.)

Of the patients in my review who had trochlear cranial nerve palsy, 77 had either a vascular cause or an undetermined cause for their palsies. Given the prognosis for recovery and the lack of dire underlying disease in these cases of trochlear cranial nerve palsy, the clinicians who treat older patient populations are clearly able to be reassuring, provided the diagnosis is secure.

Similarly, among the 108 patients who had abducens cranial nerve palsy in my review, the average age was 57 years. Of these, 46 had microvascular causes only. This number surpasses all previous and current Mayo Clinic series, and I believe it to be the highest of any published number. Combined with the 30 patients with undetermined causes, more than two thirds of all patients over 55 years of age with abducens cranial nerve palsy will have a benign diagnosis and a good prognosis.

Richards, Jones, and Younge confirm the high recovery rate among vascular and undetermined causes among all patients with oculomotor palsy, which was first reported in 1981.[3] Among those patients older than 55 years, temporizing is eminently practicable; cost-conscious physicians may carefully follow up their patients clinically, instead of initially obtaining expensive neuroimaging studies.

JAMES A. RUSH, M.D.
Tampa, Florida

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Reply

EDITOR:

As Dr. Rush points out, the older age groups tend to have a more benign prognosis, which is emphasized in our study as well. The average age of our patients was 49 years, whereas in Dr. Rush's group the average age was mark-

edly older (that is, 61½ years). Accordingly, the recovery rate from these causes was higher. Those patients in the younger age group are more likely to have a determined cause, and for the most part, by that we mean one of the nonmicrovascular causes. We certainly agree with Dr. Rush's comment that the older patient with the isolated ocular palsy should be followed up and treated with temporization because most will recover spontaneously.

We have a further study (unpublished data, Sylvia Kodsi, M.D., and Brian R. Younge, M.D.) involving the adolescent age group within this same population in which the causes are less benign. Thus, the investigation in a younger patient should by more aggressive.

We thank Dr. Rush for the emphasis on this particular point, and his ideas are certainly promulgated at the Mayo Clinic.

B. W. RICHARDS, M.D.
F. R. JONES, M.D.
B. R. YOUNGE, M.D.
Rochester, Minnesota

Apraclonidine and Argon Laser Trabeculoplasty

EDITOR:

We read with interest the recently published study, "Apraclonidine and argon laser trabeculoplasty," by P. C. Holmwood, R. D. Chase, T. Krupin, L. F. Rosenberg, J. M. Ruderman, B. A. Tallman, D. E. Brodstein, H. Chopra, and M. Goldenfeld (Am. J. Ophthalmol. 114:19, July 1992). Because argon laser trabeculoplasty is a procedure that sometimes has postoperative complications, we congratulate the authors on their fine work on an important subject.

In citing our pilot study on the subject,[1] the authors state, "Although treatment with topical pilocarpine reduces trabeculoplasty-induced intraocular pressure increase, many patients undergoing glaucoma laser procedures are already being treated with this and other antiglaucoma medications. This may account for the inability of these drugs to have a major effect on reducing laser-induced intraocular pressure increases."

However, our study showed that pilocarpine hydrochloride 4% given immediately after argon laser trabeculoplasty was effective in reducing the incidence of postlaser pressure increase regardless of whether the patients were using pilocarpine preoperatively or not. Our study was done before apraclonidine was available. However, we often use pilocarpine 4% immediately after argon laser trabeculoplasty because of the tremendous price difference between the two drugs, price being increasingly more important for our patients.

STEVEN OFNER, M.D.
JOHN R. SAMPLES, M.D.
E. MICHAEL VAN BUSKIRK, M.D.
Portland, Oregon

References

1. Ofner, S., Samples, J. R., and Van Buskirk, E. M.: Pilocarpine and the increase in intraocular pressure after trabeculoplasty. Am. J. Ophthalmol. 97:647, 1984.

Reply

EDITOR:

Drs. Ofner, Samples, and Van Buskirk reported that topical administration of pilocarpine 4% immediately after argon trabeculoplasty reduced laser-induced increases in intraocular pressure, compared to eyes not receiving pilocarpine therapy.[1] Although their letter states that this effect was independent of prelaser pilocarpine therapy, their report does not make this differentiation.

A comparison of our results (and those in numerous other studies on this topic) with the pilot report of Drs. Ofner, Samples, and Van Buskirk shows that apraclonidine is superior to pilocarpine in preventing intraocular pressure increases after laser trabeculoplasty. Apraclonidine treatment results in a greater reduction in intraocular pressure (−16% at one hour and −24% at two hours postoperatively) than pilocarpine (no change at one hour and −14% at two hours postoperatively). Moreover, although these authors report that pilocarpine reduces the frequency of hypertensive responses (the actual magnitude was not reported), apraclonidine again appears to be superior. They report that 36% of pilocarpine-treated eyes had a pressure increase at one hour and 18% at two hours postoperatively. In our report, a 1- to 5-mm Hg increase in pressure occurred in 17% of apraclonidine-treated eyes one hour after trabeculoplasty and in only 7% of eyes two hours after treatment.

As stated in our published report, we agree with Drs. Ofner, Samples, and Van Buskirk

that topical pilocarpine reduces trabeculoplasty-induced intraocular pressure increases. Pilocarpine is less costly, but it is not as efficacious as apraclonidine in reducing this trabeculoplasty-induced complication.[2] A laser trabeculoplasty-induced increase in intraocular pressure can have a potentially deleterious effect in the glaucomatous eye. Therefore, although concern for reducing health care expenditure is appropriate, we do not believe this rationale should overshadow what is in the best interest of our patients.

P. C. HOLMWOOD, M.D.
R. D. CHASE, M.D.
T. KRUPIN, M.D.
L. F. ROSENBERG, M.D.
J. M. RUDERMAN, M.D.
B. A. TALLMAN, M.D.
D. E. BRODSTEIN, M.D.
H. CHOPRA, M.D.
M. GOLDENFELD, M.D.
Chicago, Illinois

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Molded Acrylic Mouthguard to Control Bleeding at the Hard Palate Graft Site After Eyelid Reconstruction

EDITOR:

In "Molded acrylic mouthguard to control bleeding at the hard palate graft site after eyelid reconstruction," by J. A. Mauriello, Jr., B. Wasserman, S. Allee, and L. Robinson (Am J Ophthalmol 113:342, March 1992), the authors used a case to illustrate the potential problems of hemostasis associated with harvesting hard palate grafts. Bleeding may occur either at the time of surgery, or up to several weeks postoperatively. A review of over 100 hard palate grafts performed by one of us (N.S.) over the last three years demonstrated that all problems of hemostasis are either preventable, or easily

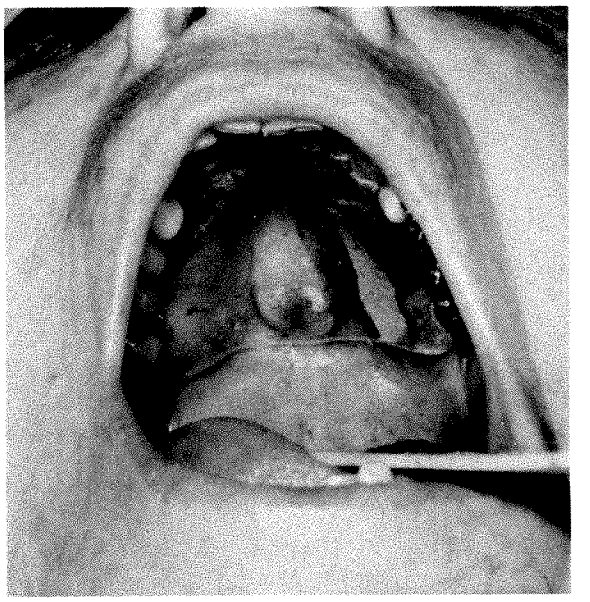


Figure (Shorr and Yenzer). Custom-made hard palate acrylic stent in place, covering donor site.

responsive to conventional therapy, which is as follows:

All routine patients have a custom-fit, self-retaining surgical stent (Figure). Any dental office can fabricate this preoperatively, and its cost is covered by most insurance plans.

The procedure is performed with monitored local anesthesia in the most cases. All aspirin and noncorticosteroidal anti-inflammatory agents are stopped for three weeks preoperatively and one week postoperatively. The hard palate area is infiltrated with 5 ml of a 2% lidocaine/1:100,000 epinephrine/75 units hyaluronidase mixture, thereby blanching and ballooning the tissue. All infiltration is anterior to the junction between the hard and soft palate. In the rare event that general anesthesia is used, a 1% lidocaine/1:100,000 epinephrine/75 units hyaluronidase mixture is infiltrated for its hemostatic effect.

The outline for the graft is marked, care being taken not to extend the incisions beyond the posterior aspect of the stent. When hard palate tissue is used as a spacer (the most common indication), the average graft size is 25 × 5 mm. However, any shape or size may be harvested.

As mentioned in the article, the large blood vessels are located adjacent to the second molar (greater and lesser palatine arteries), and just posterior to the central incisors (nasopalatine artery). The rectangular graft is outlined

with a No. 15 blade, carefully avoiding these areas, and then the incision is carried into the superficial submucosal palatine gland layer. It is important to avoid incising the mucoperiosteum, as mentioned in the article. Even more crucial, one should avoid incising the fat-gland layer (located between mucoperiosteum and the mucochondral tissue), which often contains larger vessels responsible for significant bleeding.

Hemostasis is then obtained in three steps. The first step is to coagulate all bleeding vessels with unipolar cautery. The settings required are usually higher than for conventional eyelid surgery. The assistant alternates the suction between the soft palate, to protect the airway, and the operative field. Secondly, once hemostasis is complete, ferric subsulfate solution (Monsel's solution) is applied sparingly and gently to the bed. Lastly, equal parts of dental paste (Coe-Pak) base and accelerator are mixed for approximately one minute along with one drop of eugenol (a topical anesthetic), until the soft paste reaches the consistency of putty. The surgeon's gloves are lubricated with an ointment to aid in handling the sticky substance. By using a combination of digital pressure and wet cotton applicators, the putty is packed into the site so as to lie flush with the wound edges. Putting in a mound will cause the stent to fit improperly. Denture adhesive cream is applied to the side of the stent that contacts the hard palate mucosa, except in the area of the graft site, in order to help maintain its position for several days. The longer the packing stays in place, the more comfortable is the patient. Our experience does not support the statement that the packing will control bleeding.

Postoperatively, the patient is instructed to leave the stent in place two days, then to rinse with chlorhexidene gluconate oral rinse. Thereafter, the stent can be worn or omitted, depending on each patient's preference. All hot beverages and foods are avoided for one week. The patients are instructed that if any oral bleeding occurs, to place the ball of the thumb against the graft site and suck the thumb for 30 minutes. The graft site is usually fully healed within two to three weeks.

The hard palate mucochondral graft is an excellent composite tissue for use in eyelid reconstruction. One might conclude, based on the study of Maurillo and associates that significant bleeding is an anticipated complication associated with harvesting the grafts. We appreciate the excellent review of how to manage this problem, and the useful modification of a mouthguard to keep pressure on the bleeding site. Based on over 100 cases since 1989, we have never encountered a problem which did not respond to conventional treatment. We hope this correspondence puts a perspective on how infrequently uncontrollable hemorrhaging is encountered.

NORMAN SHORR, M.D.
YOASH R. ENZER, M.D.
Los Angeles, California

Reply

EDITOR:

We agree with Drs. Shorr and Enzer that bleeding rarely occurs after harvesting of the hard palate grafts; indeed, our patient was unusual in that he had severe bleeding from subsequent oral surgery on the cheek area. After extensive hematologic reexamination, he was found to have a mild platelet abnormality despite normal bleeding, prothrombin, and partial thromboplastin times. We discovered the acrylic mouthguard was an extremely simple and effective method for controlling bleeding in this difficult unusual circumstance.

J. A. MAURILLO, JR., M.D.
B. WASSERMAN, B.A.
S. ALLEE, B.A.
L. ROBINSON, D.M.D.
Newark, New Jersey

Sudden Retinal Manifestations of Intranasal Cocaine and Methamphetamine Abuse

EDITOR:

In the article "Sudden retinal manifestations of intranasal cocaine and methamphetamine abuse," by R. T. Wallace, G. C. Brown, W. Benson, and A. Sivalingham (Am. J. Ophthalmol. 114:158, August 1992), the authors described a patient who developed a central retinal artery occlusion after using cocaine intranasally. They speculated that either arterial spasm or severe transient hypertension may have led to occlusion of the retinal artery. We have seen a similar case that occurred shortly after a man smoked crack cocaine.

A 42-year-old man had painless loss of vi-

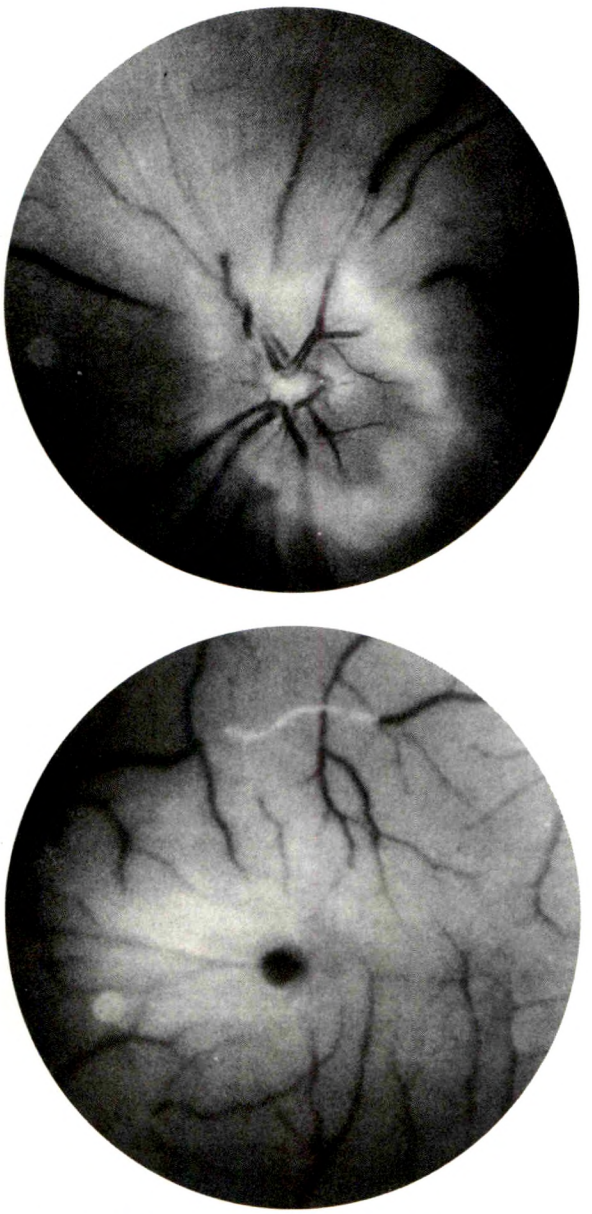


Figure (Zeiter and associates). Fundus photographs of the left eye of a crack cocaine user show edematous optic nerve (top) and whitening of the posterior pole with a foveal cherry-red spot (bottom).

sion in his left eye one hour after smoking crack cocaine. His ocular and medical histories were unremarkable. Visual acuity was R.E.: 20/20 and L.E.: hand motions. A relative afferent pupillary defect was present in the left eye. The anterior segment was normal in each eye, and the intraocular pressure by applanation tonometry was R.E.: 17 mm Hg in the right eye and 18 mm Hg in the left eye. Ophthalmoscopy disclosed a normal right fundus and an edematous optic nerve with whitening of the posterior pole and a foveal cherry-red spot in the left fundus (Figure). Fluorescein angiography of the left eye showed nonperfusion of the retinal vasculature, confirming the diagnosis of central retinal artery occlusion.

Cocaine use has been associated with a number of medical problems, many of which are life-threatening.[1] Abuse of crack cocaine, the alkaloid form of cocaine, has now reached epidemic proportions in most large urban areas and has been found to have several ocular complications.[2-4] Crack cocaine and intranasal cocaine abuse should be considered as part of the differential diagnosis for retinal vascular occlusion, especially in relatively young, otherwise healthy patients.

JOHN H. ZEITER, M.D.
Stockton, California
DONNA M. CORDER, M.D.
Dearborn, Michigan
MATHEW P. MADION, M.D.
Traverse City, Michigan
JOHN G. McHENRY, M.D.
Lavonia, Michigan

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BOOK REVIEWS

Edited by Mark J. Mannis, M.D.

Ocular Pathology. A Color Atlas, ed. 2. By Myron Yanoff and Ben S. Fine. New York, New York, Raven Press, 1992. 260 pages, index, illustrated. $110

Reviewed by ROBERT FOLBERG
Iowa City, Iowa

In the preface to the first edition of this book, the authors stated that gross pathologic specimens and photomicrographs were best studied in color. The authors never intended to substitute the present volume for their own more comprehensive textbook (Ocular Pathology: A Text and Atlas) or other encyclopedic texts, but rather as a supplement with a rich offering of color illustrations to inclusive reference texts.

This second edition is physically larger (the book has grown from a shelf-sized volume of 7.5 × 9 inches to a coffee table-sized book of 10 × 12.25 inches). It may be more difficult to store this new edition on a shelf, but the larger page makes it even easier to study the illustrations and photographs that are the focus of this volume.

The book is divided into 18 chapters. It begins with the scientific basis of pathology, including inflammation and trauma and moving on to the pathology of various anatomic locations. Each chapter has an introduction of several paragraphs of basic text. This new edition adds a brief review of anatomy and histology to each of the chapters, based on anatomic location (for example, eyelids or conjunctiva). Each chapter concludes with a brief selection of references (some as recent as 1991), although there is no attempt to cite these references in the text or the illustration legends.

The authors have added more than 70 new illustrations to this edition and have replaced other photographs used previously. The quality of most photographs is excellent. Although some photographs taken at low magnification are a bit out of focus, the use of such suboptimal photographs appears to be limited to one-of-a-kind illustrations of rare conditions that are difficult to obtain. Curiously, the legends omit the magnification of photomicrographs, information that might lend some perspective to the novices.

The authors make use of colorful tables and cartoons to illustrate basic pathologic principles. The multicolored cartoons, done in the popular style of Scientific American sketches, are lucid. The authors frequently provide thumbnail-sized sketches of their gross photographs and photomicrographs; the sketches are labeled, leaving the photographs themselves unmarred. This format permits the reader to look at the picture without the distractions of arrows and other pasted-on legends. Some readers may spend more time studying the labeling of the sketch and trying to match the sketch to the photographs than actually studying the photograph.

Some ophthalmic pathologists questioned the accuracy of the brief legends used in the first edition. Some of the classification schemes cited by the authors may be a out of date. However, the authors emphasize that this is not a primary textbook. Readers (especially residents-in-training) who use this as a primary text (a shortcut) to learning ophthalmic pathology will be missing much information, whereas those who use this color atlas to augment their studies will be enriched by it.

Color Atlas of Ophthalmic Surgery. Oculoplastic Surgery. Edited by David T. Tse. Philadelphia, Pennsylvania, J. B. Lippincott Company, 1992. 498 pages, index, illustrated. $195

Reviewed by ALLEN M. PUTTERMAN
Chicago, Illinois

This new book is filled with up-to-date information on how to do popular oculoplastic surgical procedures. It is part of a series entitled Color Atlas of Ophthalmic Surgery, which has dealt with topics such as strabismus, cataracts,

corneal and refractive surgery, glaucoma, and retina. As an atlas, the book provides brief descriptions, illustrations, and color photographs. Its scope is not comprehensive; it does not attempt to document the results, successes, or failures of the various procedures. One drawback to its limited scope is that it does not explain why the techniques described are better than alternative procedures that are not described.

As with all multi-authored books, some chapters are extremely well written and comprehensive (for example, "Socket Reconstruction"), and others are weak (for example, "Anatomy" and "Fundamental Techniques").

I especially liked the details on esoteric and less important oculoplastic procedures that other texts either omit or describe superficially. These subjects include eyelid laceration repair, punctoplasty, nasal lacrimal duct probing, browplasty, tarsorrhaphy, temporal artery biopsy, exenteration, gold weight placement, eyelid reanimation with the palpebral spring, and Mohs micrographic surgery. The beginning oculoplastic surgeon should appreciate tips on how to hold a Stryker saw in a lateral orbitotomy or the most likely source of bleeding when attempting to achieve hemostasis in the orbit.

The text is easy to follow because one illustrator did all the illustrations. In several chapters, however, the illustrations are upside down, preventing the reader from being able to digest the material easily. This is especially confusing in the chapters on ectropion and tumor. Some chapters are well illustrated but others do not have enough illustrations. The anatomy chapter is difficult to follow because of the lack of illustrations. The chapters on transconjunctival blepharoplasty and Mohs micrographic surgery could also be enhanced with more illustrations.

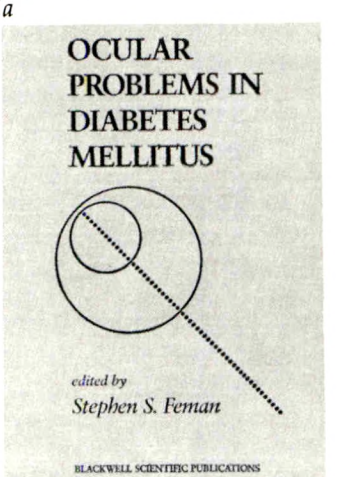
Photographs that warrant special mention include those in the chapter on orbital decompression depicting a skull being decompressed by the removal of the medial wall and floor of the orbit. It is easy to appreciate the procedure and extent of bone removal in a way that I believe has not been previously described. The inclusion of preoperative and postoperative computed tomography scans is effective.

The chapter on eyelid reanimation with a palpebral spring is outstanding. Robert Levine probably has the greatest experience wit this operation and has shared in detail his successful technique. I believe that this is the first text that thoroughly describes the hydroxyapatite implant, which is useful in replacing orbital volume after enucleation.

Overall, I highly recommend this text for all surgeons who perform oculoplastic surgery.

Ocular Problems in Diabetes Mellitus. Edited by Stephen S. Feman. Cambridge, Massachusetts, Blackwell Scientific Publications, Inc., 1992. 287 pages, index, illustrated. $79.95

Reviewed by MARK J. MANNIS
Sacramento, California



The increasing trend toward subspecialization in ophthalmology has had a positive and a negative impact on our noble branch of medicine. The degree of technical sophistication that may be achieved by the clinician immersed solely in the management of glaucoma, corneal diseases, or vitreoretinal diseases is unparalleled in the history of eye care. Conversely, the focused ophthalmologist often compartmentalizes to the extent that areas of eye disease outside the purview of that physician's interest gradually become terra incognita. However, certain diseases because they are protean in their manifestations, attract the attention of every ophthalmologist, whether general practitioner or a focused subspecialist. Diabetes mellitus is just such a disease.

In this text, Stephen Feman has provided us with a remarkable collection of 12 chapters that review the pathophysiologic and clinical manifestations of diabetes as it affects every aspect of ocular function. Diabetes is often thought of in terms of retinopathy only. This book reminds us of the widespread ocular ramifications of the

disease; indeed, only three of the 12 chapters deal with vitreoretinal disease.

The book begins with a lengthy chapter on the epidemiologic aspects of ocular problems in diabetes mellitus. Much of this chapter is devoted to a review of the Wisconsin epidemiologic study of diabetic retinopathy. However, the authors include data from other epidemiologic studies on the subject, providing the reader with thorough and well-documented data on the incidence and progression of visual impairment in diabetes. This chapter is followed by an excellent chapter outlining the general medical principles of diabetic care and a chapter on diabetic nephropathy, worthwhile reading for any ophthalmologist who needs a refresher in general medical principles in management of the disease.

The remainder of the volume deals directly with manifestations of diabetes in the eye. Beginning with chapters on pathogenic mechanisms in diabetic eye disease and the histopathologic aspects of diabetic eye changes, each subsequent section approaches diabetes from a different sphere of interest. These include a chapter on neuro-ophthalmic disorders in diabetes, corneal disease, glaucoma, diabetes and the lens, background diabetic retinopathy, proliferative retinopathy, and vitreoretinal problems. As editor, and author of three of the chapters, Dr. Feman has ensured that each of the chapters contains a thorough discussion of the area-specific clinical manifestations of diabetes, relating these to the pathogenetic mechanisms of the disease. Particularly notable is the chapter on diabetic keratopathy by Carolyn Parrish, which provides a superb review of the literature on the subject and lucidly outlines the important clinical manifestations and their management.

This is a book in which every ophthalmologist will find sections of interest. For the generalist, it holds a wealth of useful information. For the focused subspecialist, it is a valuable resource. It will certainly be of singular use to the diabetologist who must understand the disease from the point of view of its ocular ramifications. The editor and authors of this book have afforded us a practical collection of chapters on diabetes, which are complete in their treatment of basic mechanisms as well as clinical manifestations and their management.

Current Practice in Ophthalmology. Edited by Andrew P. Schachat. St. Louis, Missouri, Mosby Year Book, Inc., 1992. 403 pages, Index, Illustrated. $85

Reviewed by WING CHU
New York, New York

Practicing ophthalmologists are routinely exposed to a wide variety of publication formats in the daily mail. On the one hand, there are refereed journals with critical detail; and on the other there are the tabloid publications with screaming headlines. Their respective styles appeal to specific audiences. There is, however, a definite need for a concisely written text that addresses current ophthalmological topics in a no-nonsense format.

Current Practice in Ophthalmology successfully bridges the gap between the varieties of publication styles. Many of the chapters are written by experts in their fields. Illustrations are of excellent quality. Most of the selected topics would be of interest to practicing ophthalmologists; and although the editor readily admits that the text is not encyclopedic, it still rates as a good compendium of current relevant topics.

The book is divided into five parts. Part I, "Current Practice," consists of 22 well-selected topics. Noteworthy are the chapters on AIDS, radial keratotomy, astigmatism management, sutured intraocular lenses, and foldable intraocular lenses. The chapters on management of the swollen disk, magnetic resonance imaging, cyclosporine, and treatment of retinal breaks are also excellent. These topics alone make the book worthwhile.

The remainder of the book is divided into four shorter sections. Part II, "The Evolution of Current Practice," has five chapters. The chapters on laser treatment of various glaucomas, retinopathy of prematurity, and acute retinal necrosis are well done. Unfortunately, the chapter of phacoemulsification is disappointing. In Part III, "Controversy in Current Practice," only two areas of controversy are discussed: types of contact lenses and laser wavelength selection. Certainly there are more than two areas of controversy in ophthalmology. In my opinion, this section is rather slim.

The two remaining sections, "Grand Rounds" and "Literature Commentary," are appendages that do not fit the format of the rest of the book. Although most of this text deals with each topic in a comprehensive fashion, these two sections tend to be sketchy.

In summary, the majority of the book fulfills the goals of the editor. I recommend it to the practicing ophthalmologist.

Management and Care of the Cataract Patient. Edited by Frank J. Weinstock. Cambridge, Massachusetts, Blackwell Scientific Publications, Inc., 1992. 359 pages, index, illustrated. $89.95

Reviewed by WILLIAM SIMCOE
Tulsa, Oklahoma

This is a well-written, entertaining, up-to-date and informative book whose stated scope is not just cataract surgery, but the cataract patient as a whole. It includes and goes well beyond anesthesia, techniques of cataract surgery, intraocular lens implantation and removal, and management of complications. The scholarship is impressive. The 50 contributors are experienced and obviously know their material.

The book begins with a comprehensive history of the cataract operation up to the era of modern surgery. There is a poignant account of earlier cataract surgery on several famous artists, Monet, Daumier, and Cassatt, which evokes a feeling of sadness for those patients and their frustrated surgeons. One can only imagine the difficulties and uncertainties before our era of incredible progress and success in the surgical restoration of vision.

Cataractogenesis is discussed relative to risk factors including heredity, diabetes, ultraviolet radiation, and various medications, as well as techniques for evaluation of anticataract therapy.

There are excellent chapters on cataract surgery in patients with glaucoma and other anterior segment diseases, postcataract inflammation and endophthalmitis, corneal decompensation, cystoid macular edema, prevention of postoperative astigmatism, and accommodation after surgery. The causes, consequences, and rehabilitation of permanent postoperative low vision are well outlined. One chapter analyzes 1,300 eyes obtained post mortem with all types of intraocular lenses, and concisely summarizes the advantages of capsular fixation which this study supports. An attorney describes medicolegal risks of litigation and the additional threats of administrative sanction, that is, expulsion from participation in third-party reimbursement plans, revocation or abridgement of hospital privileges, and limitation or loss of the license to practice. Guidelines are given for informed consent, minimizing malpractice exposure, preparation for an administrative hearing, what to do if you are sued, and uses and potential abuses of the National Practitioner Data Bank. There is a chapter on diagnostic coding and billing, third-party and Medicare facility reimbursement, the 1990 Budget Reconciliation Act, peer review and medical necessity.

Extensive coverage of the problems of AIDS includes data on risk of exposure and preventive measures.

There are some beautiful color plates, although one of them misidentifies a type of posterior chamber lens in an autopsy specimen.

This book contains an amazing and comprehensive amount of information. The editor is to be congratulated on his editorial design, the scope and intent of the book, as well as the choice of excellent contributors who made his goal a reality.

Computerized Perimetry. A Simplified Guide, ed. 2. By Marc F. Lieberman and Michael V. Drake. Thorofare, New Jersey, Slack, Inc., 1992. 216 pages, index, illustrated. $50

Reviewed by ROBB R. SCHRADER
Louisville, Kentucky

The strength of this book lies in its purpose and organization. With our current generation of computerized perimeters, Drs. Lieberman and Drake have given us a practical and efficient way to master visual field testing with these machines.

Theory and fundamentals are appropriately covered in the first two chapters. Although the book concerns itself primarily with discussion of the Octopus and Humphrey machines, the

reader is given a clear understanding of Hans Goldmann's concepts and his perimeter. Descriptions of the Octopus and Humphrey perimeters occupy separate chapters. Interesting background information on the hardware is provided, but the emphasis is on the various software programs and their features.

Many will find the chapters, "Selecting the Appropriate Test," "Interpreting the Results," and "Statistically Assisted Interpretation," particularly useful, because they concisely demystify the decision of which test to run and the decoding of the printout that follows. The final two chapters cleverly use brief case histories intended to gauge the reader's understanding of many of the concepts discussed earlier in the book.

The table of contents and the index are well done and, given the clear page layout and the strategic use of the bold print, it is easy to refer quickly to any topic covered. Summaries are found at the end of several chapters as well as lists of suggested readings. Most of the illustrations are clear, with the exception of some of the small print and numbers on several of the reproduced visual fields.

I was glad to see that the need for clinical perspective was emphasized often. This perspective is enhanced by helpful comments derived from the authors' experience peppered throughout the text. Those interested in neuro-ophthalmology will not be disappointed with this book, even though its clinical focus is almost exclusively on glaucoma. It should enjoy a wide audience among ophthalmologists in training and in practice.

ABSTRACT DEPARTMENT

Edited by George B. Bartley, M.D.

Corneal storage medium preservation with defensins. Schwab, I. R.*, Dries, D., Cullor, J., Smith, W., Mannis, M., Reid, T., and Murphy, C. J.: Cornea 11:370, 1992.

Contaminated donor corneal tissue may cause keratitis and endophthalmitis after penetrating keratoplasty, despite the use of gentamicin or other antimicrobial agents in corneal storage media. Most antibiotics interfere with cell multiplication and thus may be ineffective in sterilizing storage media at 4 C, a temperature at which most common pathogenic bacteria are not dividing. Defensins, which are cysteine-rich and arginine-rich peptides contained within the macrophage and neutrophil granules of some mammals, have been considered as possible alternatives to antibiotics because of their broad-spectrum in vitro activity against a variety of bacteria, fungi, and viruses. The authors studied the antimicrobial effect of a synthetic defensin, rabbit neutrophil peptide-1, in a chondroitin sulfate–based corneal storage medium. At a concentration of 200 μg/ml, the defensin successfully killed 99.9% (the limit of the assay) of *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa* at temperatures of 4 C, 23 C, and 37 C, respectively. Neutrophil peptide-1 may be useful as a nonantibiotic preservative in corneal storage media.—George B. Bartley

*Department of Ophthalmology, University of California at Davis, 1603 Alhambra Blvd., Sacramento, CA 95816.

Corneal topographic changes over time after radial keratotomy. Moreira, H., Fasano, A. P., Garbus, J. J., Lee, M., and McDonnell, P. J.*: Cornea 11:465, 1992.

The authors used corneal topography to determine the evolution of corneal curvature after radial keratotomy for myopia. Eleven eyes in ten patients were studied. Three of the patients had previously worn soft contact lenses, but in each case the lenses had been discontinued at least six months preoperatively. Four to eight radial incisions were made to a depth of 100% of the thinnest of four paracentral corneal thicknesses; the central clear zone varied from 3 to 4.5 mm. Shortly after radial keratotomy, the central 0.5 to 1.0 mm of the cornea was relatively steeper than the paracentral cornea (similar to results found in human eye-bank models) and the peripheral cornea was steeper than the preoperative measurements. By 45 days postoperatively, however, the central and midperipheral cornea had flattened. After three months or more, the central cornea had flattened to a greater degree than had the paracentral cornea, and the peripheral cornea was flatter than preoperatively. The corneal flattening progressed nonuniformly and unpredictably, which may explain the multifocal lens effect that occurs in some patients. Wound healing may involve relaxation or sliding of severed stromal lamellae. The authors believed that the eye-bank eye model is useful for studying the acute effects of radial keratotomy but has limitations in determining long-term results.—George B. Bartley

*Doheny Eye Institute, 1355 San Pablo St., Los Angeles, CA 90033.

Evaluation of corneal topography. Past, present and future trends. Morrow, G. L., and Stein, R. M.*: Can. J. Ophthalmol. 27:213, 1992.

Although relatively simple instruments to measure corneal curvature have been available for many years, more accurate quantitation has become possible during the last decade with the advent and evolution of computer-assisted corneal topographic analysis. The authors succinctly described the normal corneal topography, reviewed the basic mechanics of keratometry, keratoscopy, photokeratoscopy, and computerized corneal topography, and discussed the clinical applications of current topographic systems. Computer-assisted corneal topography is useful in diagnosing keratoconus, for planning refractive surgical procedures, and in fitting contact lenses over unusually shaped corneas. Future applications of compu-

terized photokeratoscopy may include intraoperative topography, custom-fitting of contact lenses, ray-tracing analysis, and computerized holography and three-dimensional corneal imaging.—George B. Bartley

*M. K. Bochner Eye Institute, 40 Prince Arthur Ave., Toronto, Ontario M5R 1A9, Canada.

Improved detection of disease progression in ocular cicatricial pemphigoid. Tauber, J., Jabbur, N., and Foster, C. S.*: Cornea 11:446, 1992.

Ocular cicatricial pemphigoid is a systemic autoimmune disease that may cause visual loss from corneal scarring. Earlier in the clinical course, disease progression is manifested by subconjunctival cicatrization, fibrosis, and symblephara. The authors postulated that the staging systems currently in use may be insensitive in detecting disease progression, possibly causing delays in instituting systemic chemotherapy. The original Foster system classifies the disease into one of four stages. Stage I includes eyes with chronic conjunctivitis and subepithelial scarring and fibrosis, but without forniceal foreshortening or symblephara; Stage II includes eyes with forniceal foreshortening but without symblephara; Stage III includes eyes with symblephara; and Stage IV is marked by ankyloblepharon and an immobile globe. The four stages of the Mondino system parallel the progressive loss of the inferior fornix depth. The original Foster system does not grade increases in forniceal foreshortening or in symblephara extension, whereas the Mondino system does not include the appearance of new symblephara in the absence of progressive forniceal loss. The new proposed classification combines the strengths of each system by adding four subdivisions (a = 0% to 25%, b = 25% to 50%, c = 50% to 75%, d = 75% to 100%) within the original Foster system to describe the percentage of loss of the inferior fornix depth (in Stage II) or the percentage of horizontal involvement by symblephara (in Stage III).—George B. Bartley

*Immunology Service, Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114.

Apraclonidine hydrochloride as an adjunct to timolol maleate therapy. Blasini, M., and Shields, M. B.*: J. Glaucoma 1:148, 1992.

Twenty-four patients with primary open-angle glaucoma, uncontrolled on timolol 0.5% twice daily, were randomly assigned adjunctive therapy with either 0.0625%, 0.125%, or 0.25% apraclonidine or the vehicle of apraclonidine in a prospective, parallel, double-masked, 3-month study. All three concentrations of apraclonidine were associated with additional mean pressure reductions from baseline of 2-4 mm Hg at the majority of testing periods for the duration of the study. No clinically significant ocular or systemic adverse reactions were observed with the addition of apraclonidine to timolol therapy.—Authors' abstract

*Duke University Eye Center, Box 3802, Durham, NC 27710.

Reduced ocular hypotensive effect of topical β-blockers in glaucoma patients receiving oral β-blockers. Gross, F. J.*, and Schuman, J. S.: J. Glaucoma 1:174, 1992.

Previous reports concerning the efficacy of topical β-blocker therapy when used concomitantly with systemic β-blockers had conflicting conclusions. The authors reviewed the medical records of 27 patients who were already using systemic β-blockers to treat hypertension, cardiac arrhythmia, or angina pectoris at the time that topical β-blocker therapy was instituted for glaucoma, and compared the changes in intraocular pressure with 28 control patients with glaucoma. The average intraocular pressure–lowering effect of topical β-blockers was statistically significantly reduced in patients taking systemic β-blockers at all studied intervals (zero to two months [P = .02], three to six months [P = .00], and seven to 12 months [P = .01]). Additionally, treatment with a topical nonselective β-blocker caused a significantly smaller decrease in intraocular pressure in patients using systemic nonselective β-blockers than in patients using a systemic β-1 antagonist [P = .01]. The authors concluded that the efficacy of topical β-blockers is reduced in patients

with glaucoma who concomitantly are being treated with systemic β-blockers. Adding a topical nonselective β-blocker to a β-1 selective systemic agent may be therapeutically useful. Alternatively, topical miotic therapy may be a good first choice in patients who are using systemic β-blockers.—George B. Bartley

*3235 Academy Ave., Suite 101, Portsmouth, VA 23703.

Digital indocyanine green videoangiography and choroidal neovascularization. Yannuzzi, L. A.*, Slakter, J. S., Sorenson, J. A., Guyer, D. R., and Orlock, D. A.: Retina 12:191, 1992.

Indocyanine green dye has advantages over sodium fluorescein in delineating the choroidal circulation during angiography because of its absorption and emission in the near-infrared range (which allows penetration through normal ocular pigments such as melanin and xanthophyll) and because it binds strongly to plasma proteins (which reduces dye leakage through the fenestrated choriocapillaris). The authors used digital indocyanine green videoangiography to study 129 patients with exudative age-related macular degeneration and ill-defined or suspected choroidal neovascularization. In 50 patients (39%), the choroidal vascular lesions could be reclassified as "well-delineated or so-called classic" choroidal neovascularization after angiography with indocyanine green dye. The technique was particularly useful in identifying neovascularization beneath large, serous retinal pigment epithelial detachments and in eyes on which laser photocoagulation had been performed. Indocyanine green angiography was well-tolerated and was associated with fewer side effects than with fluorescein. The authors believe that digital indocyanine green videoangiography is a useful adjunct in the examination, classification, and treatment of patients with ill-defined choroidal neovascularization associated with age-related macular degeneration.—George B. Bartley

*Retinal Center, Manhattan Eye, Ear and Throat Hospital, 210 E. 64th St., New York, NY 10021.

Congenital hypertrophy of retinal pigment epithelium in patients with colonic polyps associated with cancer family syndrome. Houlston, R. S.*, Fallon, T., Harocopos, C., Williams, C. B., Davey, C., and Slack, J.: Clin. Genet. 42:16, 1992.

Of the several dominantly inherited family cancer syndromes that are associated with an increased tendency to develop colonic polyps, adenomatous polyposis coli carries the greatest risk of colorectal cancer. The presence of three or more patches of congenital hypertrophy of the retinal pigment epithelium is a common feature of this disorder, which is unique among family cancer syndromes in having an extracolonic biomarker. Karyotype analysis and linkage studies, however, have suggested that variation of the adenomatous polyposis coli gene locus on the long arm of chromosome 5 also may be involved in other inherited colorectal cancer syndromes. The authors identified four or more patches of congenital hypertrophy of the retinal pigment epithelium in three of 21 unrelated first-degree relatives of patients with cancer family syndrome and colonic adenomas, but without adenomatous polyposis coli. They concluded that the retinal finding should be interpreted cautiously as a marker for adenomatous polyposis coli in asymptomatic individuals in whom pedigree information is not available.—George B. Bartley

*Wessex Cardiothoracic Centre, Southampton General Hospital, Southampton SO9 4XY, United Kingdom.

Head injury in very young children. Mechanisms, injury types, and ophthalmologic findings in 100 hospitalized patients younger than 2 years of age. Duhaime, A. C.*, Alario, A. J., Lewander, W. J., Schut, L., Sutton, L. N., Seidl, T. S., Nudelman, S., Budenz, D., Hertle, R., Tsiaras, W., and Loporchio, S.: Pediatrics 90:179 1992.

Head injury in the youngest age group is distinct from that occurring in older children or adults because of differences in mechanisms, injury thresholds, and the frequency with which the question of child abuse is encoun-

tered. To analyze some of these characteristics in very young children, the authors prospectively studied 100 consecutively admitted head-injured patients 24 months of age or younger who were drawn from three institutions. Mechanism of injury, injury type, and associated injuries were recorded. All patients underwent ophthalmologic examination to document the presence of retinal hemorrhages. An algorithm incorporating injury type, best history, and associated findings was used to classify each injury as inflicted or accidental. The results confirmed that most head injuries in children younger than 2 years of age occurred from falls, and while different fall heights were associated with different injury types, most household falls were neurologically benign. Using strict criteria, 24% of injuries were presumed inflicted, and an additional 32% were suspicious for abuse, neglect, or social or family problems. Intradural hemorrhage was much more likely to occur from motor vehicle accidents and inflicted injury than from any other mechanism, with the latter being the most common cause of mortality. Retinal hemorrhages were seen in serious accidental head injury but were most commonly encountered in inflicted injury. The presence of more serious injuries associated with particular mechanisms may be related to a predominance of rotational rather than translational forces acting on the head.—Authors' abstract

*Department of Neurosurgery, Children's Hospital, 34th and Civic Center Blvd., Philadelphia, PA 19104.

Whiplash and its effect on the visual system. Burke, J. P.*, Orton, H. P., West, J., Strachan, I. M., Hockey, M. S., and Ferguson, D. G.: Graefes Arch. Clin. Exp. Ophthalmol. 230:335, 1992.

Ophthalmologists occasionally are asked to render a medicolegal opinion regarding the ocular sequelae and prognosis of an injury. The authors studied 39 patients who were examined within one week of a whiplash injury to identify possible ophthalmic complications related to this type of trauma. Ten patients (25.6%) had ocular signs and symptoms that commenced shortly after the accident. Decreased convergence and accommodation were present in six patients, superior oblique muscle paresis was diagnosed in two patients, diminished stereopsis was found in one patient, and bilateral vitreous detachments occurred in one patient. Symptoms resolved in all but two of the patients within nine months (one patient with decreased convergence and accommodation and the patient with vitreous detachments). The authors concluded that whiplash injuries are associated with a higher incidence of ophthalmic complications than had been previously reported, but noted that the ocular abnormalities are generally mild and have a good prognosis.—George B. Bartley

*Department of Ophthalmology, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

Management of suspected giant cell arteritis. A decision analysis. Buchbinder, R.*, and Detsky, A. S.: J. Rheumatol. 19:1220, 1992.

The formulation of a treatment strategy for a patient with possible giant cell arteritis depends on the following five factors: the likelihood of disease, the estimated risk of no treatment, the estimated benefit of therapy, the estimated risk of therapy, and the reliability and validity of available diagnostic procedures. The authors used a relative scale of the value of information and risk-benefit analysis (the number of cases of monocular blindness averted/the number of cases of severe side effects from corticosteroid treatment) to compare different therapeutic strategies for patients with giant cell arteritis. The four strategies were as follows: to treat no patients, to treat all patients, to treat only patients in whom temporal artery biopsy confirmed giant cell arteritis, or to perform temporal artery biopsy and treat all patients irrespective of the result. Withholding treatment is preferred only if the likelihood of giant cell arteritis is less than 2%, an unusual scenario in the authors' opinions: "Even a normal erythrocyte sedimentation rate (ESR) in the setting of reasonable clinical evidence would place the likelihood of disease above this threshold." The "biopsy and treat positive cases" strategy is most useful for patients in whom there is an intermediate likelihood (50%) of disease. The "biopsy but treat irrespective of the result" strategy is preferred when the probability of giant cell arteritis is 81% or more. Empiric therapy with corticosteroids without

performing a biopsy is preferred only if the likelihood of disease exceeds 90% and the dysutility related to treating under diagnostic uncertainty is low when the probability of disease is high. The "management of suspected giant cell arteritis should be guided by the results of temporal artery biopsy across a wide likelihood of disease."—George B. Bartley

*Room 650, Turner Wing, Wellesley Hospital, 160 Wellesley St. E., Toronto, Ontario M4Y 1J3, Canada.

Presenting features and outcomes in patients undergoing temporal artery biopsy. A review of 98 patients. Chmelewski, W. L., McKnight, K. M., Agudelo, C. A., and Wise, C. M.*: Arch. Intern. Med. 152:1690, 1992.

The authors reviewed the medical records of 98 patients who underwent temporal artery biopsy over a five-year interval to define the spectrum of initial clinical features and eventual outcomes. Thirty patients had a positive result for giant cell arteritis, whereas in 68 patients the result was negative. Patients in whom giant cell arteritis was confirmed by biopsy had a significantly increased incidence of headache (28 patients [93%] vs 42 patients [62%], P = .003), jaw claudication (15 patients [50%] vs 12 patients [18%], P = .003), and previous polymyalgia rheumatica (seven patients [23%] vs two patients [3%], P = .004); the sensitivity and specificity of these indicators, however, were relatively low. The erythrocyte sedimentation rate and the prevalence of prior treatment with corticosteroids were similar between the two groups. Treatment with corticosteroids in the 30 patients in whom temporal arteritis was confirmed by biopsy yielded excellent results without serious side effects, but mild flares in disease activity after one year of therapy were common. No patients required cessation of corticosteroid therapy during the first year, but treatment was discontinued in six of 19 patients at two years and in five of 11 patients at three years. Diagnoses in the 68 patients in whom temporal arteritis was not confirmed by biopsy included neurologic diseases in 15 patients, polymyalgia rheumatica without temporal arteritis in 14 patients, and other inflammatory rheumatologic diseases in ten patients. The authors concluded that initial clinical features are seldom helpful in predicting biopsy results, that treatment is effective but frequently toxic, that late disease-related complications are rare, and that most patients require long-term low-dose corticosteroid therapy.—George B. Bartley

*Section on Rheumatology, Bowman Gray School of Medicine, Medical Center Blvd., Winston-Salem, NC 27157.

Midbrain syndromes of Benedikt, Claude, and Nothnagel. Setting the record straight. Liu, G. T.*, Crenner, C. W., Logigian, E. L., Charness, M. E., and Samuels, M. A.: Neurology 42:1820, 1992.

In contrast to Weber's syndrome, which is universally described as comprising ipsilateral oculomotor nerve palsy and contralateral hemiparesis, the definitions of the eponymic oculomotor nerve fascicular syndromes of Benedikt, Claude, and Nothnagel vary considerably in current neuro-ophthalmology textbooks. The authors reviewed the original descriptions of these syndromes to clarify their respective components. Benedikt's syndrome includes oculomotor palsy, contralateral hemiparesis, and contralateral involuntary movements or tremor; the lesion is thought to involve the oculomotor nerve fascicle, the cerebral peduncle, and possibly the substantia nigra and the red nucleus. Claude's syndrome comprises oculomotor nerve palsy, contralateral ataxia, asynergy, and dysdiadochokinesia, and occasional trochlear nerve palsy and sensory loss from a lesion of the oculomotor nerve fascicle, red nucleus, superior cerebellar peduncle, and possibly the trochlear nerve, medial lemniscus, and medial longitudinal fasciculus. Nothnagel's syndrome results from a lesion of the superior and inferior colliculi and includes bilateral (but usually asymmetric) oculomotor nerve palsies of varying degree, gait ataxia, and possibly nystagmus.—George B. Bartley

*Bascom Palmer Eye Institute, P.O. Box 016880, Miami, FL 33101.

Selective loss of optic nerve β-tubulin in vincristine-induced blindness. Munier, F.*, Perentes, E., Herbort, C. P., Uffer, S., and Biollaz, J.: Am. J. Med. 93:232, 1992.

The chemotherapeutic agent, vincristine, may cause neurologic dysfunction that typically is dose-dependent and reversible. Side effects result from depolymerization of neurotubules (causing impaired axonal transport) and from neurofibrillary degeneration. The authors described the case of a 25-year-old woman who had been treated with vincristine, doxorubicin, and bleomycin for disseminated Kaposi's sarcoma associated with acquired immunodeficiency syndrome. The patient's vision before chemotherapy was normal, but bilateral optic atrophy and blindness developed within seven months. No other neurologic deficits were identified other than moderate distal sensory neuropathy. Histologic examination at autopsy disclosed complete atrophy of the retinal ganglion cells and advanced optic nerve gliosis and myelin rarefaction. Immunohistochemical staining of the optic nerve identified axonal injury that was characterized by a negative reaction for class III β-tubulin isotype and the 200-kd neurofilament subunit. The authors concluded that the optic atrophy represented vincristine toxicity and that the reaction is idiosyncratic, dose-independent, and irreversible in some instances.—George B. Bartley

*Hôpital Jules Gonin, Université de Lausanne, Lausanne, Switzerland.

Immunosuppressive treatment of Graves' ophthalmopathy. Wiersinga, W. M.*: Thyroid 2:229, 1992.

The ophthalmic manifestations of Graves' disease have been treated by a variety of immunosuppressive modalities, including corticosteroids, cyclosporine, intravenous immunoglobulin, azathioprine, ciamexon, cyclophosphamide, plasmapheresis, and retrobulbar irradiation. Immunosuppression seldom cures the eye disease, but it usually is helpful in relieving soft-tissue inflammation, is moderately efficacious in improving extraocular muscle dysfunction, and typically is ineffective in reducing proptosis. The author reviewed the benefits and risks of immunosuppressive treatments and concluded that systemic corticosteroid therapy is the most effective option, but that it is associated with the highest incidence of side effects. Radiotherapy may be useful if corticosteroid treatment fails; however, its use in diabetic patients or in patients being treated with chemotherapy is limited because of an increased risk of radiation retinopathy. Cyclosporine has limited application but may be effective in combination with prednisone. Intravenous immunoglobulin is efficacious, but expense and concerns about the transmission of infectious agents limit its use. Immunosuppressive therapy is most effective when administered during the active (inflammatory) phase of the disease, allowing subsequent rehabilitative ophthalmic surgical procedures to be performed earlier.—George B. Bartley

*Department of Endocrinology, Academisch Medisch Centrum, F5-258, Meibergdreef 9, 1105 A2 Amsterdam, The Netherlands.

Reconstruction of the lacrimal excretory system. Huang, T. T.*, Sasaki, K., and Nozaki, M.: Plast. Reconstr. Surg. 90:399, 1992.

The reestablishment of tear drainage in the presence of diffuse canalicular obstruction or severe traumatic nasolacrimal disruption typically is attempted with a conjunctivodacryocystorhinostomy and Jones tube. Problems with the alloplastic device, however, have led surgeons to attempt to achieve tear drainage with a fistula of autologous tissue. The authors described a technique in which a tubed conjunctival flap (originating from the inferior palpebral and forniceal conjunctiva and extending "2 mm anterior to the limbus") was used as a tear conduit to the nasal cavity, the inferior portion of the lacrimal sac, or the maxillary antrum. Twenty-four bypass procedures were performed in 20 patients, most of whom had nasolacrimal obstruction from trauma. Epiphora and conjunctivitis were relieved in 19 patients, but "no attempts were made to assess quantitatively the efficacy of tear drainage." No ocular complications were reported.—George B. Bartley

*326 Market St., Galveston, TX 77550.

Severe orbital infection as a complication of orbital fracture. Silver, H. S., Fucci, M. J., Flanagan, J. C., and Lowry, L. D.*: Arch. Otolaryngol. Head Neck Surg. 118:845, 1992.

The authors reviewed the medical records of 130 patients who were hospitalized for treatment of an orbital infection during a 15-year period. Of 30 patients who had true orbital (postseptal) cellulitis, three patients developed the infection shortly after sustaining an orbital fracture from blunt trauma. Two of the patients were immunocompromised (diabetes mellitus in a 54-year-old woman and chronic alcohol and intravenous drug abuse in a 41-year-old man); the third patient was a 9-year-old boy. All three patients recovered after treatment with intravenous antibiotics and surgical drainage. Because the most common factor that contributes to the development of orbital cellulitis is paranasal sinusitis, which may predate or follow an orbital fracture, the authors recommended that all patients who sustain blunt orbital trauma undergo computed tomographic scanning and should be treated with prophylactic antibiotics. Corticosteroids, which have been advocated by some investigators to diminish orbital soft-tissue swelling after orbital blowout fractures, should be prescribed with caution.—George B. Bartley

*Department of Otolaryngology-Head and Neck Surgery, Thomas Jefferson University Hospital, 90 Walnut St., Third Floor, Philadelphia, PA 19107.

A controlled trial of a single dose of azithromycin for the treatment of chlamydial urethritis and cervicitis. Martin, D. H.*, Mroczkowski, T. F., Dalu, Z. A., McCarty, J., Jones, R. B., Hopkins, S. J., Johnson, R. B., and the Azithromycin for Chlamydial Infections Study Group: N. Engl. J. Med. 327:921, 1992.

Chlamydia trachomatis is the most common sexually transmitted pathogen in the United States. The usual treatment is a seven-day, multidose regimen of oral tetracycline, doxycycline, or erythromycin, but previous reports have demonstrated that many patients do not complete the course of therapy. The authors conducted a multicenter study in which patients were randomly assigned to treatment to compare the efficacy of a single 1-g dose of oral azithromycin (the prototype of a new group of antibiotics, the azalides) to a seven-day course of doxycycline (100 mg, orally, twice a day). Five of 141 patients (4%) treated with azithromycin and three of 125 patients (2%) treated with doxycycline did not respond to therapy. Chlamydial cultures that were obtained three to five weeks after treatment were positive in none of 112 patients in the azithromycin group and in one of 102 patients treated with doxycycline. The rates of bacteriologic cure were similar for female and male patients. Mild to moderate drug-related side effects, primarily gastrointestinal symptoms, occurred in 41 of 237 patients (17%) treated with azithromycin and 43 of 220 patients (20%) treated with doxycycline. The authors concluded that azithromycin administered in a single 1-g dose is as effective as a standard seven-day course of doxycycline for the treatment of uncomplicated genital chlamydial infections.—George B. Bartley

*Department of Medicine, Section of Infectious Diseases, Louisiana State University, 1542 Tulane Ave., New Orleans, LA 70112.

Acyclovir. A decade later. Whitley, R. J.*, and Gnann, J. W., Jr.: N. Engl. J. Med. 327:782, 1992.

In this review article (100 references), the authors summarized the mechanism of action, pharmacologic characteristics, spectrum of activity, and toxicity of acyclovir, which is the most widely prescribed and clinically effective antiviral drug in contemporary use. Acyclovir selectively inhibits the replication of herpes simplex virus types 1 and 2 and varicella-zoster virus by competing with deoxyguanosine triphosphate as a substrate for viral DNA polymerase. The drug inhibits Epstein-Barr virus replication at high concentrations, but is ineffective against cytomegalovirus. Acyclovir is available in topical, oral, and intravenous preparations. The bioavailability of acyclovir after oral administration is approximately 15% to 30%, and 85% of the compound is excreted unchanged in the urine. Indications for acyclovir therapy include genital herpes simplex virus infections, mucocutaneous herpes simplex virus infections in immunocompromised patients, herpes simplex virus encephalitis, neonatal herpes simplex virus infections, and varicella or herpes zoster infections in normal or immunocompromised hosts. Topical acyclovir therapy has been used for ocular herpes simplex virus infections, but was not superior

to trifluridine. Although treatment of herpes zoster ophthalmicus with acyclovir reduces the incidence of keratitis and uveitis, it has no effect on postherpetic neuralgia, which occurs in approximately 45% of patients. Acyclovir-resistant isolates of both herpes simplex and herpes zoster viruses have been identified, but the mutant strains were sensitive to vidarabine and foscarnet. Toxic reactions to acyclovir are unusual; however, reversible renal dysfunction, agitation, hallucinations, disorientation, tremors, and myoclonus have been reported after intravenous infusion.—George B. Bartley

*653 Children's Hospital Tower, 1600 Seventh Ave. S., Birmingham, AL 35294-0011.

Pharmaceutical promotions. A free lunch? Waud, D. R.*: N. Engl. J. Med. 327:351, 1992.

The author of this thought-provoking editorial shared his views on the ethical implications of the acceptance by physicians of gifts or funds from pharmaceutical firms, an amount estimated to be $165 million per year. "Gifts," according to guidelines published by the American College of Physicians, "should not be of substantial value." The author believed that such gifts are no different from bribes and reasoned that "just as you cannot be a little bit pregnant, you cannot be a partial bribe taker." As regards the subsidization of scientific meetings or continuing medical education courses, the author concluded that the practice is unacceptable because, ultimately, the money "comes out of the pockets of patients"; to accept such funds was considered inconsistent with the physician's responsibility to act in the patient's best interests. Finally, the author believed that there is "no role whatsoever for drug advertising . . . if, on Monday, someone in San Francisco comes up with a new treatment that clearly reduces the mortality or morbidity from some disease, people in Boston will know about it by Tuesday." The author recommended that the medical community use the Hippocratic oath as its frame of reference when deciding whether to accept gifts or funds from the pharmaceutical industry, and develop appropriate guidelines voluntarily before they are legislated.—George B. Bartley

*University of Massachusetts Medical School, Worcester, MA 01655.

NEWS ITEMS

Send News Items to
American Journal of Ophthalmology
435 N. Michigan Ave., Suite 1415
Chicago, IL 60611

The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

The Association of European Community University Professors of Ophthalmology

The Association of European Community University Professors of Ophthalmology has recently founded the European Community Ophthalmic Research Association. The aim of the Association is to encourage basic research pertaining to the eye and its functions. Prof. Manfred Spitznas of the Department of Ophthalmology at the University of Bonn is executive director.

Medical College of Wisconsin: Advanced Vitreoretinal Symposium in Honor of Thomas M. Aaberg

The Eye Institute at the Medical College of Wisconsin will sponsor the Advanced Vitreoretinal Symposium in honor of Thomas M. Aaberg, April 15–17, 1993, at the American Club in Kohler, Wisconsin. For further information, write Dennis P. Han, M.D., 8700 W. Wisconsin Ave., Milwaukee, WI 53226; telephone (414) 257-5341.

Hawaiian Eye Foundation: Meeting Site Changed

The site of the 14th Annual Royal Hawaiian Eye Meeting on Jan. 16–22, 1993, has been changed. The meeting was scheduled to be held on the island of Kauai, but because of hurricane damage, the meeting has been moved to the Ritz Carlton Kapalua Maui Resort. For additional information, write to Mary Charles and Associates, 2334 S. King St., Suite 205, Honolulu, HI 96826; telephone (808) 942-9655; fax (808) 949-1273.

Manhattan Eye, Ear & Throat Hospital: Clinical Decisions in Glaucoma—Challenges and Changes

The Department of Ophthalmology of the Manhattan Eye, Ear & Throat Hospital will hold a course, Clinical Decisions in Glaucoma—Challenges and Changes, Feb. 27, 1993, in New York City. For further information, write Kimberly Corbin, Department of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3760; fax (212) 753-7699.

The Emory Clinic: 30th Annual Emory-Grady Alumni Postgraduate Conference

The Emory Clinic will hold its 30th Annual Emory-Grady Alumni Postgraduate Conference, Feb. 5 and 6, 1993, at the J. W. Marriott Hotel Buckhead, in Atlanta, Georgia. For further information, write the Office of Continuing Medical Education, Emory University School of Medicine, 1440 Clifton Rd. N.E., Atlanta, GA 30322; telephone (404) 727-5695.

New York Academy of Medicine: Third Annual Eyelid Rejuvenation Symposium

The New York Academy of Medicine and the Foundation for the Facially Disfigured will sponsor the Third Annual Eyelid Rejuvenation Symposium, May 14 and 15, 1993, in New York City. For more information, write Francine Leinhardt, Professional Meeting Planners, Inc., 116 E. 63rd St., New York, NY 10021; telephone (212) 338-9200 ext. 2776; fax (212) 832-9126.

Sarasota Retina Institute: Seventh Annual Sarasota Vitreoretinal Update Course

The Sarasota Retina Institute will hold the Seventh Annual Sarasota Vitreoretinal Update Course, Jan. 26–29, 1993, at the Longboat Key Club in Sarasota, Florida. For more information, write Lois Delagrange, Sarasota Retina Institute, 3400 Bee Ridge Rd., Sarasota, FL

34239; telephone (813) 921-5335; fax (813) 921-1741.

Scheie Eye Institute: Keratoconus—Is There Anything New?

The Scheie Eye Institute at the University of Pennsylvania will present a half-day seminar, Keratoconus—Is There Anything New?, Jan. 16, 1993, in Philadelphia, Pennsylvania. For more information, write Charlotte Beurer, Office of Continuing Medical Education, Scheie Eye Institute, Myrin Circle, 51 N. 39th St., Philadelphia, PA 19104; telephone (215) 662-8141.

Scheie Eye Institute and Wills Eye Hospital: Retina and Choroid 1993—New Controversial Topics

The Scheie Eye Institute at the University of Pennsylvania and the Department of Oncology at the Wills Eye Hospital will cosponsor a seminar, Retina and Choroid 1993—New Controversial Topics, Jan. 9, 1993, at the Scheie Eye Institute in Philadelphia, Pennsylvania. For further information, write Charlotte Beurer, Office of Continuing Medical Education, Scheie Eye Institute, Myrin Circle, 51 N. 39th St., Philadelphia, PA 19104; telephone (215) 662-8141.

Stanford University: Intraocular and Crystalline Lens Problems—A Practical Approach to Management

The Department of Ophthalmology at the Stanford University School of Medicine will sponsor a course, Intraocular and Crystalline Lens Problems—A Practical Approach to Management, Feb. 20, 1993, in Stanford, California. For more information, write Mark S. Blumenkranz, M.D., Continuing Education, Department of Ophthalmology A-157, Stanford Medical Center, Stanford, CA 94305-5308; telephone (415) 725-7269.

Stanford University: Perfluorocarbons in Ophthalmology

The Department of Ophthalmology at the Stanford University School of Medicine will sponsor a course, Perfluorocarbons in Ophthalmology, Jan. 16, 1993, in Stanford, California. For more information, write Mark S. Blumenkranz, M.D., Continuing Education, Department of Ophthalmology A-157, Stanford Medical Center, Stanford, CA 94305-5308; telephone (415) 725-7269.

University of Illinois at Chicago: Winter Glaucoma Symposium and Practice Management Seminar

The UIC Eye Center at the University of Illinois at Chicago will sponsor the Eighth Winter Glaucoma Symposium and Practice Management Seminar, Feb. 14–16, 1993, in Grand Cayman, British West Indies. For additional information, write Laura Perez, UIC Eye Center, 1855 W. Taylor St., Chicago, IL 60612; telephone (312) 413-7391.

University of Utah: Advances in Craniofacial, Oculoplastic, and Facial Aesthetic Surgery

The School of Medicine at the University of Utah will offer a course, Advances in Craniofacial, Oculoplastic, and Facial Aesthetic Surgery, Jan. 27–30, 1993, at the Cliff Lodge in Snowbird, Utah. For further information, write Richard L. Anderson, M.D., University of Utah School of Medicine, Health Sciences Center, Salt Lake City, UT 84132; telephone (801) 581-8664.

Frank B. Walsh Society: Annual Meeting

The Annual Meeting of the Frank B. Walsh Society will be held March 13 and 14, 1992, in New York City. For additional information, write Jacqueline S. Winterkorn, M.D., North Shore University Hospital-Cornell University Medical College, 300 Community Dr., Manhasset, NY 11030; telephone (516) 562-2663.

Joint Commission on Allied Health Personnel in Ophthalmology: New Commissioners

The following new commissioners have been appointed to the Joint Commission on Allied

Health Personnel in Ophthalmology from its membership organizations: John D. Fisher, of Temple, Texas, has been appointed as a representative of the Association of Veterans Administration Ophthalmologists, replacing Kenneth Zaslow; Richard L. Lindstrom, of Minneapolis, Minnesota, has been appointed by the American Ophthalmological Society, replacing Brian R. Younge; C. Gail Summers, of Minneapolis, Minnesota, is a new representative of the Association of University Professors in Ophthalmology, replacing Alfonse A. Cinotti; and M. Edward Wilson, Jr., of Charleston, South Carolina, is a representative of the Association of University Professors in Ophthalmology, replacing Richard D. Cunningham.

Fight for Sight: Scientific Research Awards

Mildred Weisenfeld, founder and executive director of Fight for Sight, Inc., and James Wright, president of the National Society to Prevent Blindness, announce the scientific research awards approved for funding during 1992–1993.

Grants-in-Aid

Enrico Cagliero, M.D., Dept. of Biochemistry and Cell Biology, Eye Research Institute, Boston, MA. DNA Damage and Repair in Diabetic Retinopathy. $8,000. (Awarded in Honor of Bob Hope.)

Janet Davis, M.D., Dept. of Ophthalmology, Bascom Palmer Eye Institute, Miami, FL. Comparison of Intraocular Antibody and Viral Genome Detection as Diagnostic Aids in Necrotizing Retinitis in AIDS. $11,000. (Funded by the Hearst Foundation.)

Charles L. Densmore, Ph.D., Center for Biotechnology, Baylor College of Medicine, The Woodlands, TX. Site Directed Antibodies to Neurotransmitter Transporters in the Vertebrate Retina. $11,000.

Richard D. Dix, Ph.D., Dept. of Ophthalmology, Bascom Palmer Eye Institute, Miami, FL. Pathogenesis of Cytomegalovirus Retinitis in Mice Immunosuppressed by Retrovirus Co-Infection. $11,000. (Awarded in Honor of Bob Hope.)

Kathleen J. Doane, Ph.D., Dept. of Pathology, Robert Wood Johnson Medical School, Piscataway, NJ. Integrin-Mediated Interactions During Development of the Corneal Stroma. $10,000.

Evan B. Dreyer, M.D., Ph.D., Dept. of Ophthalmology, Massachusetts Eye and Ear Infirmary, Boston, MA. Excitatory Amino Acids in Glaucoma. $11,000.

Thomas W. Gardner, M.D., Dept. of Ophthalmology, Pennsylvania State University, Hershey, PA. The Sodium Pump and Diabetic Retinopathy. $9,000. (Awarded in Memory of Alexander P. and Mary E. Hirsch.)

Robert E. Hausman, Ph.D., Dept. of Biology, Boston University, Boston, MA. Cell Signaling Control of Retinal Development. $11,000.

Jonathan J. Henry, Ph.D., Dept. of Cell and Structural Biology, University of Illinois, Urbana, IL. The Molecular Basis of Lens Development. $11,000.

Michelle A. Kurpakus, Ph.D., Dept. of Anatomy/Cell Biology, Wayne State University, Detroit, MI. Keratin Expression in Cultured Conjunctival Epithelium. $7,000.

Kenneth K. Kwong, Ph.D., NMR Research, Massachusetts Eye and Ear Infirmary, Boston, MA. Functional Magnetic Resonance Imaging of the Visual Cortex. $10,400. (Awarded in Honor of Dr. Charles A. Perera.)

Delwin T. Lindsey, Ph.D., Center for Cognitive Science, Ohio State University, Columbus, OH. Molecular and Psychophysical Studies of Human Color Vision. $11,000.

Richard L. Maas, M.D., Ph.D., Dept. of Medicine, Brigham & Women's Hospital, Boston, MA. Molecular Genetic Analysis of the Pax-6 Gene in Aniridia. $10,500.

Darrell R. McCaslin, Ph.D., Dept. of Chemistry, Rutgers University, Newark, NJ. Conformational Properties of the Phosphorylation Site of Rhodopsin. $9,300.

Alexandra C. Newton, Ph.D., Dept. of Chemistry, Indiana University, Bloomington, IN. Phosphorylation of Rhodopsin by Protein Kinase C. $9,500.

John M. Nickerson, Ph.D., Dept. of Ophthalmology, Emory University, Atlanta, GA. Establishment of a System to Produce Human IRBP. $11,000.

Heywood M. Petry, Ph.D., Dept. of Psychology, University of Louisville, Louisville, KY. Color and Luminance Sensitivity in Primary Open-Angle Glaucoma: Tests of Early Magno and Parvo Channel Deficits. $10,500.

John D. Porter, Ph.D., Dept. of Anatomy and Neurobiology, University of Kentucky, Lexington, KY. Ontogeny of the Innervation Pattern of Extraocular Muscle: A Mechanistic Study Using

Organotypic Nerve/Muscle Co-Culture and Confocal Microscopy. $11,000. (Awarded in Memory of Dr. Hermann M. Burian and wife Gladys.)

Kathryn A. Rich, Ph.D., Doheny Eye Institute, Los Angeles, CA. Role of the Extracellular Matrix Protein Thrombospondin in the Developing Retina. $11,000.

Postdoctoral Fellowships

Anumanthan Anukanth, Ph.D., Dept. of Chemistry, Massachusetts Institute of Technology, Cambridge, MA (H. Gobind Khorana, Ph.D., Sponsor). Molecular Basis for the Functional Assembly of Rhodopsin. $14,000. (Awarded in Memory of Alexander P. and Mary E. Hirsch.)

Shiming Chen, Ph.D., Dept. of Ophthalmology, Johns Hopkins University, Baltimore, MD (Donald J. Zack, M.D., Ph.D., Sponsor). Regulation of Rhodopsin Gene Expression: In Vivo Studies. $14,000. (Awarded in Memory of Silas Adelsheim.)

Ricardo Fujita, Ph.D., Dept. of Ophthalmology, W. K. Kellogg Eye Center, Ann Arbor, MI (Anand Swaroop, Ph.D., Sponsor). In Search of Candidate Genes for X-Linked Eye Diseases. $14,000.

Steven H. Hensley, Ph.D., Dept. of Ophthalmology, Cullen Eye Institute, Houston, TX (Samuel M. Wu, Ph.D., Sponsor). Ganglion Cell Neurotransmission and Retinal Dysfunction. $14,000.

Chang-Jin Jeon, Ph.D., Dept. of Neurosurgery, Massachusetts General Hospital, Boston, MA (Richard H. Masland, Ph.D., Sponsor). Morphologies of the Unidentified Amacrine Cells. $14,000. (Awarded in Honor of Bob Hope.)

Valery E. Krupnik, Ph.D., Dept. of Neurosurgery, Massachusetts General Hospital, Boston, MA (Linda L. Y. Chun, Ph.D., Sponsor). Trophic Factors for Mammalian Retinal Ganglion Cells. $14,000.

Romesh Kumar, Ph.D., Dept. of Laboratory Medicine, University of Washington, Seattle, WA (Thomas R. Fritsche, M.D., Ph.D., Sponsor). Use of Polymerase Chain Reaction and Gene Probes in the Diagnosis of Acanthamoeba Keratitis. $14,000.

Shoji Kuriyama, M.D., Ph.D., Dept. of Ophthalmology, Jules Stein Eye Institute, Los Angeles, CA (Michael O. Hall, Ph.D., Sponsor). Analysis of the Defect in cAMP Production in the RCS Rat Pigment Epithelial Cells. $14,000.

Steven A. Odrich, M.D., Dept. of Ophthalmology, Mount Sinai Medical Center, New York, NY (Steven Podos, M.D., Sponsor). Indocyanine Green Enhanced Diode Laser Cyclophotocoagulation. $10,000. (Awarded in Honor of Elsie K. Sloate.)

Marcie W. Pospichal, Ph.D., Dept. of Psychology, Vanderbilt University, Nashville, TN (Jon H. Kaas, Ph.D., Sponsor). Effects of the Albino Mutation on Visual System Structure and Function. $14,000.

Haohua Qian, Ph.D., Dept. of Cellular and Developmental Biology, Harvard University, Cambridge, MA (John E. Dowling, Ph.D., Sponsor). Modulation of Neurotransmitter Responses in Retinal Ganglion Cells. $12,000.

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Student Fellowships

Rajpaul S. Attariwala, Dept. of Biomedical Engineering, Northwestern University, Evanston, IL (Matthew R. Glucksberg, Ph.D., Sponsor). Effect of Intraocular Pressure on Retinal Vascular Pressure. $1,500.

Amish M. Bhakta, Dept. of Ophthalmology, Jules Stein Eye Institute, Los Angeles, CA (Ben J. Glasgow, M.D., Sponsor). Study of Lacrimal Gland Pathology. Purification and Sequencing of Lacrimal Specific Protein. $1,500.

Brian P. Bosworth, Dept. of Ophthalmology, North Shore University Hospital, Manhasset, NY (Sam Packer, M.D., Sponsor). Histopathology of Choroidal Melanoma Treated With Boron Neutron Capture Therapy. $1,000. (Supported by the Burroughs Wellcome Fund.)

Nabil Boutros, Dept. of Ophthalmology, W. K. Kellogg Eye Center, Ann Arbor, MI (Bret A. Hughes, Ph.D., Sponsor). Mechanism of Na+ Transport Across the Retinal Pigment Epithelium. $875. (Awarded in Memory of James Thurber.)

Nancy M. Greene, Dept. of Chemistry, Indiana University, Bloomington, IN (Alexandra C. Newton, Ph.D., Sponsor). A Study of the Phosphorylation of Rhodopsin by Protein Kinase C. $1,500. (Funded by Canon, U.S.A.)

Christopher A. Hunsinger, Dept. of Human Genetics, University of Pennsylvania, Philadelphia, PA (Dwight Stambolian, M.D., Ph.D., Sponsor). Isolation of the Mouse X-Linked Cataract Gene (Xcat). $1,500.

Susmitha P. Kolli, Dept. of Ophthalmology and Visual Science, The University of Chicago, Chicago, IL (Ramesh C. Tripathi, M.D., Ph.D., F.A.C.S., Sponsor). Receptors for Transferrin in Trabecular Cells. $1,500.

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Mahnaz Nouri, Dept. of Ophthalmology, Massachusetts Eye and Ear Infirmary, Boston, MA (C. Stephen Foster, M.D., F.A.C.S., Sponsor). Corneal Wound Healing Following Excimer Laser Anterior Keratectomy. $1,125. (Awarded in Memory of Norma Newman Cohen.)

Emmanuel U. Nzekwe, Ph.D., Dept. of Ophthalmology, Stanford University, Stanford, CA (David Maurice, Ph.D., Sponsor). Ophthalmic Drug Penetration in the Elderly. $1,500. (Awarded in Honor of Neil and Donna Weisman.)

Julian D. Perry, Dept. of Ophthalmology, Columbia University, New York, NY (Peter Gouras, M.D., Sponsor). The Effects of a Retinal Palmitate Deficient Diet in the RCF Rat. $1,500. (Awarded in Memory of Albert G. and Herman B. Mosler.)

Johanna L. Phillips, Dept. of Biology, Boston University, Boston, MA (Robert E. Hausman, Ph.D., Sponsor). The Effect of Retinoic Acid on Cognin-Mediated Differentiation of Chick Retinal Neurons. $1,500.

Darin S. Smith, Dept. of Ophthalmology, Duke University Medical Center, Durham, NC (Diane L. Hatchell, Ph.D., Sponsor). Does Neutrophil Activation by Platelet Activating Factor Increase Vascular Permeability of Retinal Endothelial Cell Monolayers? $1,500. (Supported by the Burroughs Wellcome Fund.)

Jeffrey A. Tuvlin, Dept. of Ophthalmology & Visual Sciences, Washington University, St. Louis, MO (Nalini S. Bora, Ph.D., Sponsor). Identification and Characterization of P-36 in Human Eye. $1,500. (Awarded in Memory of James Thurber.)

Personals

Lawrence F. Jindra

Lawrence F. Jindra of Floral Park, New York, has been awarded a 1992–1993 White House Fellowship. Dr. Jindra, an attending ophthalmic surgeon and director of the Northport Veterans Affairs Medical Center Glaucoma Consultation Unit and a clinical assistant professor at the State University of New York, was selected as one of 15 White House Fellows in recognition of his leadership, professional and intellectual achievements, and dedication to his community.

Burton Kushner

Burton Kushner received the Heed Award of the Society of Heed Fellows at the 1992 meeting of the American Academy of Ophthalmology. Dr. Kushner was a Heed Fellow in pediatric ophthalmology at the Bascom Palmer Institute (1973–1974). Dr. Kushner received the M.D. degree from Northwestern University in 1949 and served a residency at the University of Wisconsin Hospitals in Madison. He is now clinical professor of ophthalmology at the University of Wisconsin Medical School.

Bradley R. Straatsma, chairman of the Board of Directors of the Heed Foundation, made the presentation. The Society of Heed Fellows numbers over 500 practicing ophthalmologists who received grants from the Heed Foundation for fellowships in clinical ophthalmology. Froncie A. Gutman of the Cleveland Clinic Foundation is founder and secretary-treasurer of the Society of Heed Fellows.

Govindappa Venkataswamy

Govindappa Venkataswamy of India is the 1992 recipient of the Lighthouse Pisart Vision Award. Dr. Venkataswamy has saved the eyesight of countless numbers of people by demonstrating the link between vitamin A deficiency and childhood blindness, by devising a hospital system that provides cataract surgery to vast numbers of patients, and by pioneering eye camps that deliver professional vision care to even the most remote villages in India.

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SUBJECT INDEX

NOTE: Abstract Index follows Author Index

A

Abducens nerve
Acquired oculomotor, trochlear, and abducent cranial nerve palsies in pediatric patients, 568
Causes and prognosis in 4,278 cases of paralysis of the oculomotor, trochlear, and abducens cranial nerves (correspondence), 777

Abscess
Calcified intraocular abscess simulating retinoblastoma (letter), 227

Acetazolamide
Anaphylactic shock and death after oral intake of acetazolamide (letter), 367

Acquired immunodeficiency syndrome
Acquired immunodeficiency syndrome and ophthalmology: the first decade, 86
Bilateral panuveitis, sebopsoriasis, and secondary syphilis in a patient with acquired immunodeficiency syndrome (letter), 773
Frosted branch angiitis associated with cytomegalovirus retinitis (correspondence), 514
Glove perforations in ophthalmic surgery, 397
In situ detection of human herpesvirus 6 in retinitis associated with acquired immunodeficiency syndrome (letter), 375
Intravitreal foscarnet for cytomegalovirus retinitis in a patient with acquired immunodeficiency syndrome, 742
Ocular toxoplasmosis in human immunodeficiency virus-infected patients, 130
Ultrastructure of human immunodeficiency virus in corneal epithelial scraping (letter), 633
Xanthomonas maltophilia endophthalmitis after implantation of sustained-release ganciclovir (letter), 772

Acute retinal necrosis
Polymerase chain reaction for the detection of the Varicella-zoster genome in ocular samples from patients with acute retinal necrosis, 603

Adduction
Recession of both horizontal recti muscles in Duane's retraction syndrome with elevation and depression of the adducted eye, 311

Aging
Corneal endothelial cytoskeletal changes in F-actin with aging, diabetes, and after cytochalasin exposure, 329
Immunohistochemical and histochemical properties of surgically excised subretinal neovascular membranes in age-related macular degeneration, 464
Severe anaphylactic reaction after indocyanine green fluorescence angiography (letter), 638
Surgical excision of subfoveal neovascular membranes in age-related macular degeneration (correspondence), 241

Amblyopia
Use of a transparent film dressing to enhance compliance with occlusion therapy for amblyopia (letter), 229

Anesthesia
Parabulbar anesthesia (letter), 776
Propofol and surgical contamination in strabismus surgery (letter), 635

Aneurysm
Development of a retinal artery macroaneurysm at the site of a previously detected retinal artery embolus (letter), 642

Angiography
Severe anaphylactic reaction after indocyanine green fluorescence angiography (letter), 638

Aniridia
Criteria to detect minimal expressivity within families with autosomal dominant aniridia, 700

Anisocoria
Idiopathic alternating anisocoria (letter), 509

Anterior segment
Ultrasound biomicroscopy of anterior segment structures in normal and glaucomatous eyes (correspondence), 516

Antibiotic
The solubility of antibiotic and corticosteroid combinations, 212

Apraclonidine
Apraclonidine and argon laser trabeculoplasty, 19
Apraclonidine and argon laser trabeculoplasty (correspondence), 778
Prophylactic use of apraclonidine for intraocular pressure increase after Nd:YAG capsulotomies (correspondence), 377

Aqueous
Aqueous dynamics in exfoliation syndrome, 473

Artery
Central retinal artery occlusion after neck irradiation (letter), 224
Development of a retinal artery macroaneurysm at the site of a previously detected retinal artery embolus (letter), 642
Sudden retinal manifestations of intranasal cocaine and methamphetamine abuse (correspondence), 780
Traumatic rupture of a persistent hyaloid artery (letter), 225

Aspergillus sp.
Six cases of scleritis associated with systemic infection, 55

Astigmatism
Photorefractive keratectomy for severe postkeratoplasty astigmatism, 429

B

Bacteria
Ciprofloxacin-resistant bacterial keratitis, 336

Behr's syndrome
Behr's syndrome and 3-methylglutaconic aciduria, 494

Beta-blocker
Short-term effects of levobunolol on ocular pulsatile flow, 280

Biomicroscopy
Ultrasound biomicroscopy of anterior segment structures in normal and glaucomatous eyes (correspondence), 516

Blepharoptosis
Ophthalmic involvement in myo-neuro-gastrointestinal encephalopathy syndrome, 322

Books and Computer Software
Atlas of Ophthalmic Surgery, volume II, Oculoplastic, Lacrimal, and Orbital Surgery, by Dutton, J. J., 651

Atlas of Orbital Surgery, by Leone, C. R., Jr., Grove, A. S., Jr., Lloyd, W. C., III, and Wojno, T. H., 381

Automated Static Perimetry, by Anderson, D. R., 110

The Basics of Neuro-ophthalmology, by Farris, B. K. (ed.), 243

The Changing Visual System. Maturation and Aging in the Central Nervous System, by Bagnoli, P., and Hodos, W. (eds.), 520

Clinical Decisions in Neuro-Ophthalmology, ed. 2, by Burde, R. M., Savino, P. J., and Trobe, J. D., 381

Color Atlas of Ophthalmic Surgery. Oculoplastic Surgery, by Tse., D. T., (ed.), 782

Computerized Perimetry. A Simplified Guide, ed. 2, by Lieberman, M. F., and Drake, M. V., 785

Corneal Alterations With Contact Lens Wear, by Rouwen, A. J. P., 520

Current Practice in Ophthalmology, by Schacht, A. P. (ed.), 784

Decision Making in Ophthalmology, by van Heuven, W. A. J., and Zwaan, J. T. (eds.), 653

Developments in Ophthalmology, vol. 24. Embryology of the Eye and Its Adnexae, by Straub, W. (ed.), 244

Diabetic Retinopathy. A Slide-Script Program, by American Academy of Ophthalmology, 520

Enzymology of the Ears, by Berta, A., 653

Essentials of Ophthalmology, by Bartley, G. B., and Liesegang, T. J., 112

The Eye in General Practice, ed. 9, by Jackson, C. R. S., and Finlay, R. D., 383

Fluorescein Angiography. Technique, Interpretation, and Application, by Nanjiani, M., 382

The Fragile Species, by Thomas, L., 652

Fundamentals of Ophthalmic Practice. Ethics and Economics. Office and Risk Management., by Kamenotzky, S. A., 653

Glaucoma Surgery, by Thomas, J. V. (ed.), 111

Grayson's Diseases of the Cornea, ed. 3, by Arffa, R. C., 518

The History of Ophthalmology, vol. 10. The First and Second Half of the Nineteenth Century (Parts 9 to 17), by Hirschberg, J., 243

Intraocular Tumors. A Text and Atlas, by Shields, J. A., and Shields, C. L., 112

The Lazy Eye. A Simulation Environment for Neuro-Ophthalmology. Computer Software, by Bregman, H. S., Ly, P. T., and Galetta, S., 651

Management and Care of the Cataract Patient, by Weinstock, F. J. (ed.), 785

Management and Treatment of Benign Cutaneous Vascular Lesions, by Tan, O. T. (ed.), 653

Manual of Systematic Corneal Surgery, by , 244

Medical Malpractice. Handling Ophthalmology Cases, by Rabin, S. M., 520

Neuro-Ophthalmology. A Practical Text, by Newman, N. M., 519

Ocular Emergencies, by Catalano, R. A., 650

Ocular Pathology. A Color Atlas, ed. 2, by Myron, Y., and Fine, B. S., 782

Ocular Problems in Diabetes Mellitus, by Feman, S. S. (ed.), 783

Optics and Refraction. A User-Friendly Guide., by Miller, D., 650

Refractive Keratotomy for Myopia and Astigmatism, by Waring, G. O., III (ed.), 110

Spanish-English, English-Spanish Medical Dictionary, by McElroy, O. H., and Grabb, L. L., 384

The Surgical Rehabilitation of Vision, by Nordon, L. T., Maxwell, W. A., and Davison, J. A. (eds.), 518

Working With Visually Impaired Young Students. A Curriculum Guide for Birth—3-Year-Olds, by Trief, E. (ed.), 244

***Brucella* sp.**
Brucellosis and uveitis (letter), 374

C

Capsulotomy
Posterior capsulotomy as a complication of indirect laser photocoagulation, 600

Prophylactic use of apraclonidine for intraocular pressure increase after Nd:YAG capsulotomies (correspondence), 377

Carbachol
Therapeutic index of pilocarpine, carbachol, and timolol with nasolacrimal occlusion, 1

Cataract
Asymmetric pigmentary glaucoma resulting from cataract formation, 484
Causes of reduced visual acuity on long-term follow-up after cataract extraction in patients with uveitis and juvenile rheumatoid arthritis, 708
Ocular findings in Cockayne syndrome, 579
Progression of nonproliferative diabetic retinopathy and visual outcome after extracapsular cataract extraction and intraocular lens implantation, 448
Racial differences in the prevalence of intraocular lens implants in the United States, 667
Results of late surgery for presumed congenital cataracts, 409
Retained lens fragments after phacoemulsification manifesting as market intraocular inflammation with hypopyon, 610
Stereopsis after congenital monocular cataract extraction, 314
Superior rectus muscle overaction after cataract extraction, 72
Total detachment of Descemet's membrane after small-incision cataract extraction (letter), 365

Central retinal artery
Central retinal artery occlusion after varicella; correction, 235

Cerebro-rhino-orbital mucormycosis
Adjunctive hyperbaric oxygen in the treatment of bilateral cerebro-rhino-orbital mucormycosis, 208

Chiasm
Spontaneous visual improvement in chiasmal gliomas, 193

Children
Acquired oculomotor, trochlear, and abducent cranial nerve palsies in pediatric patients, 568
Behr's syndrome and 3-methylglutaconic aciduria, 494
Inflammatory oribital tumor as an ocular sign of a battered child (letter), 510
Recession of both horizontal recti muscles in Duane's retraction syndrome with elevation and depression of the adducted eye, 311
Results of late surgery for presumed congenital cataracts, 409
Successful therapy for trilateral retinoblastoma, 23
Successful therapy for trilateral retinoblastoma (correspondence), 646
Successful therapy for trilateral retinoblastoma (correspondence), 647
The Tokyo metropolitan home vision screening program for amblyopia in 3-year-old children, 416
Treatment of acquired intermittent horizontal jerk nystagmus with baclofen (letter), 366

***Chlamydia* sp.**
The use of polymerase chain reaction for the detection of chlamydial keratoconjunctivitis, 685

Choroid
Choroidal neovascularization occurring within a demarcation line (letter), 101

Ciliary body
Corneoscleral, ciliary body, and vitreoretinal toxicity after excessive instillation of mitomycin C (letter), 503

Ciprofloxacin
Ciprofloxacin-resistant bacterial keratitis, 336

Cocaine
Sudden retinal manifestations of intranasal cocaine and methamphetamine abuse, 158

Cockayne syndrome
Ocular findings in Cockayne syndrome, 579

Collagen shield
The solubility of antibiotic and corticosteroid combinations, 212

Coloboma
Spontaneous retinal reattachment in a patient with persistent hyperplastic primary vitreous and an optic nerve coloboma (letter), 769

Conjunctiva
Closure of fornix-based posttrabeculectomy conjunctival wound leaks with autologous fibrin glue (letter), 221
Conjunctival concretions (letter), 640
Conjunctival involvement in paraneoplastic pemphigus, 621
Recurrence of herpetic stromal keratitis after a conjunctival flap surgical procedure (letter), 231
Trabeculectomy without conjunctival incision (correspondence), 108

Conjunctivitis
Meibomian gland function and giant papillary conjunctivitis, 188

Cornea
Bilateral radiant damage to the cornea and retina after exposure to a 700-V electric discharge (letter), 775
Clinical and histopathologic changes in the host cornea after epikeratoplasty for keratoconus, 161
Community care of corneal ulcers, 531
Contralateral occipital depression related to obstetric forceps injury to the eye, 318
Corneal endothelial cytoskeletal changes in F-actin with aging, diabetes, and after cytochalasin exposure, 329
Corneal sensitivity after photorefractive keratectomy, 51
Corneoscleral, ciliary body, and vitreoretinal toxicity after excessive instillation of mitomycin C (letter), 503
11-0 Mersilene as running suture for penetrating keratoplasty, 675

Enterococcus faecalis infection in a corneal graft (letter), 233

A new, band-shaped and whorled microcystic dystrophy of the corneal epithelium, 35

Optisol corneal storage medium, 345

Paraformaldehyde-induced keratitis after photorefractive keratectomy, 339

Progress and regression of partial corneal involvement in the iridocorneal endothelial syndrome, 171

Recurrence of herpes simplex after excimer laser keratectomy (letter), 96

Retained lens fragments after phacoemulsification manifesting as market intraocular inflammation with hypopyon, 610

Total detachment of Descemet's membrane after small-incision cataract extraction (letter), 365

Ultrastructure of human immunodeficiency virus in corneal epithelial scraping (letter), 633

Visual outcome after penetrating keratoplasty with double continuous or combined interrupted and continuous suture wound closure, 63

Corrections

Central retinal artery occlusion after varicella; correction, 235

Sculpting of hydroxyapatite implants—correction (correspondence), 380

Cortical blindness

Nonbacterial thrombotic endocarditis and cortical blindness (letter), 643

Corticosteroid

The solubility of antibiotic and corticosteroid combinations, 212

Cyclophotocoagulation

The influence of exposure duration in transscleral Nd:YAG laser cyclophotocoagulation, 560

Cyst

Hereditary microphthalmia with colobomatous cyst, 30

Mucogenic glaucoma caused by an epithelial cyst of the iris stroma (letter), 222

Vitreous pulsations, relative hypotony, and retrobulbar cyst associated with a congenital optic pit (letter), 767

Cystoid macular edema

Retinal neovascularization and cystoid macular edema in punctate albescens retinopathy (letter), 507

Cytomegalovirus retinitis

Frosted branch angiitis associated with cytomegalovirus retinitis (correspondence), 514

Intravitreal foscarnet for cytomegalovirus retinitis in a patient with acquired immunodeficiency syndrome, 742

Xanthomonas maltophilia endophthalmitis after implantation of sustained-release ganciclovir (letter), 772

D

Decompression

Torsional diplopia after transantral orbital decompression and extraocular muscle surgery associated with Graves' orbitopathy (correspondence), 239

Descemet's membrane

Total detachment of Descemet's membrane after small-incision cataract extraction (letter), 365

Diabetes mellitus

Corneal endothelial cytoskeletal changes in F-actin with aging, diabetes, and after cytochalasin exposure, 329

Neuro-ophthalmic associations and complications of diabetes mellitus, 498

Prevalence and risk factors of diabetic retinopathy among noninsulin-dependent diabetic subjects, 723

Diabetic retinopathy

Cytokines in the vitreous of patients with proliferative diabetic retinopathy, 731

Efficacy of fluid-air exchange for postvitrectomy diabetic vitreous hemorrhage, 457

Prevalence and risk factors of diabetic retinopathy among noninsulin-dependent diabetic subjects, 723

Progression of nonproliferative diabetic retinopathy and visual outcome after extracapsular cataract extraction and intraocular lens implantation, 448

Diathermy

Subretinal diathermy probe (letter), 508

Dipivefrin

Therapeutic index of epinephrine and dipivefrin with nasolacrimal occlusion, 8

Diplopia

Torsional diplopia after transantral orbital decompression and extraocular muscle surgery associated with Graves' orbitopathy (correspondence), 239

Distichiasis

Localized distichiasis after tarsorrhaphy (letter), 104

Drusen

Foveal densitometry in adult-onset diffuse drusen, 149

Duane's retraction syndrome

Recession of both horizontal recti muscles in Duane's retraction syndrome with elevation and depression of the adducted eye, 311

Dystrophy

A new, band-shaped and whorled microcystic dystrophy of the corneal epithelium, 35

E

Editorials

Divergent approaches to the management of corneal ulcers (PEPOSE, J. S., and WILHELMUS, K. R.), 630

The obligation of ophthalmic organizations to report their actions (NEWELL, F. W.), 220
The obligation of ophthalmic organizations to report their actions (correspondence), 649

***Eikenella* sp.**
Orbital cellulitis caused by *Eikenella corrodens*, 584

Embolus
Development of a retinal artery macroaneurysm at the site of a previously detected retinal artery embolus (letter), 642

Emmetropia
Intraocular lens power calculations for multifocal intraocular lenses, 405

Endocarditis
Nonbacterial thrombotic endocarditis and cortical blindness (letter), 643

Endoillumination
Macular phototoxicity caused by fiberoptic endoillumination during pars plana vitrectomy, 287

Endophthalmitis
Intraocular fluid cultures after primary pars plana vitrectomy, 697
Late-onset sterile endophthalmitis after Molteno tube implantation (letter), 771
Xanthomonas maltophilia endophthalmitis after implantation of sustained-release ganciclovir (letter), 772

Endothelium
Corneal endothelial cytoskeletal changes in F-actin with aging, diabetes, and after cytochalasin exposure, 329

Enophthalmos
Ocular findings in Cockayne syndrome, 579

***Enterococcus* sp.**
Enterococcus faecalis infection in a corneal graft (letter), 233

Epikeratoplasty
Clinical and histopathologic changes in the host cornea after epikeratoplasty for keratoconus, 161

Epinephrine
Therapeutic index of epinephrine and dipivefrin with nasolacrimal occlusion, 8

Epithelium
Mucogenic glaucoma caused by an epithelial cyst of the iris stroma (letter), 222
A new, band-shaped and whorled microcystic dystrophy of the corneal epithelium, 35

Exfoliation syndrome
Aqueous dynamics in exfoliation syndrome, 473

Eyelid
Lateral tarsorrhaphy for a noncompliant patient with floppy eyelid syndrome (letter), 367
Molded acrylic mouthguard to control bleeding at the hard palate graft site after eyelid reconstruction (correspondence), 779
Paroxysmal eyelid retractions (letter), 105
Periosteal flap for lower eyelid reconstruction (letter), 513
Preseptal cellulitis caused by *Nocardia brasiliensis* (letter), 373

F

Fibronectin
Topical fibronectin in the treatment of keratoconjunctivitis sicca, 441

Fluorouracil
Hypotonous maculopathy after trabeculectomy with subconjunctival 5-fluorouracil, 544
Results of intraoperative 5-fluorouracil supplementation on trabeculectomy for open-angle glaucoma, 737

Foscarnet
Intravitreal foscarnet for cytomegalovirus retinitis in a patient with acquired immunodeficiency syndrome, 742

Fovea
Foveal densitometry in adult-onset diffuse drusen, 149

Frosted branch angiitis
Frosted branch angiitis associated with cytomegalovirus retinitis (correspondence), 514

Frosted branch periphlebitis
Mild frosted branch periphlebitis (letter), 505

G

Ganciclovir
Xanthomonas maltophilia endophthalmitis after implantation of sustained-release ganciclovir (letter), 772

Genetics
Criteria to detect minimal expressivity within families with autosomal dominant aniridia, 700
Hereditary microphthalmia with colobomatous cyst, 30
Ocular findings in Cockayne syndrome, 579
Ultrastructural findings in an autopsy eye from a patient with Usher's syndrome type II, 748
Vogt-Koyanagi-Harada syndrome in patients with Cherokee indian ancestry, 615
X-Linked recessive familial exudative vitreoretinopathy, 145

Giant papillary conjunctivitis
Meibomian gland function and giant papillary conjunctivitis, 188

Glaucoma
Anaphylactic shock and death after oral intake of acetazolamide (letter), 367
Apraclonidine and argon laser trabeculoplasty, 19
Aqueous dynamics in exfoliation syndrome, 473
Argon laser gonioplasty in the treatment of angle-closure glaucoma, 14
The association of iridoschisis and angle-recession glaucoma (letter), 766
Asymmetric pigmentary glaucoma resulting from cataract formation, 484

Changes in optic disk characteristics and the number of nerve fibers in experimental glaucoma, 554

Hypotonous maculopathy after trabeculectomy with subconjunctival 5-fluorouracil, 544

Impending macular hole associated with topical pilocarpine (letter), 765

Late-onset sterile endophthalmitis after Molteno tube implantation (letter), 771

Low-tension glaucoma in identical twins (letter), 764

Mucogenic glaucoma caused by an epithelial cyst of the iris stroma (letter), 222

Pattern discrimination perimetry in patients with glaucoma and ocular hypertension, 297

Results of intraoperative 5-fluorouracil supplementation on trabeculectomy for open-angle glaucoma, 737

Short-term effects of levobunolol on ocular pulsatile flow, 280

Therapeutic index of epinephrine and dipivefrin with nasolacrimal occlusion, 8

Therapeutic index of pilocarpine, carbachol, and timolol with nasolacrimal occlusion, 1

Ultrasound biomicroscopy of anterior segment structures in normal and glaucomatous eyes (correspondence), 516

Visual field defects in patients with normal-tension glaucoma and patients with high-tension glaucoma, 758

Glioma
Spontaneous visual improvement in chiasmal gliomas, 193

Gonioplasty
Argon laser gonioplasty in the treatment of angle-closure glaucoma, 14

Graft
Enterococcus faecalis infection in a corneal graft (letter), 233

Molded acrylic mouthguard to control bleeding at the hard palate graft site after eyelid reconstruction (correspondence), 779

Graves' orbitopathy
Torsional diplopia after transantral orbital decompression and extraocular muscle surgery associated with Graves' orbitopathy (correspondence), 239

H

Hansen's disease
Intraocular pressure decrease in household contacts of patients with Hansen's disease and endemic control subjects, 479

Health care delivery
Community care of corneal ulcers, 531

Hemorrhage
Efficacy of fluid-air exchange for postvitrectomy diabetic vitreous hemorrhage, 457

Herpes gladiatorum
Ocular involvement in an outbreak of herpes gladiatorum, 680

Herpes simplex
Ocular involvement in an outbreak of herpes gladiatorum, 680

Reactivation of latent herpes simplex virus by excimer laser photokeratectomy, 45

Recurrence of herpes simplex after excimer laser keratectomy (letter), 96

Recurrence of herpetic stromal keratitis after a conjunctival flap surgical procedure (letter), 231

Herpes zoster
Six cases of scleritis associated with systemic infection, 55

Herpesvirus
In situ detection of human herpesvirus 6 in retinitis associated with acquired immunodeficiency syndrome (letter), 375

Hodgkin's disease
Optic neuropathy in Hodgkin's disease, 625

Human immunodeficiency virus
Frosted branch angiitis associated with cytomegalovirus retinitis (correspondence), 514

Glove perforations in ophthalmic surgery, 397

Ocular toxoplasmosis in human immunodeficiency virus-infected patients, 130

Ultrastructure of human immunodeficiency virus in corneal epithelial scraping (letter), 633

Hyaloid
Traumatic rupture of a persistent hyaloid artery (letter), 225

Hyperopia
Ocular findings in Cockayne syndrome, 579

Hypertension
Pattern discrimination perimetry in patients with glaucoma and ocular hypertension, 297

Hypopyon
Retained lens fragments after phacoemulsification manifesting as market intraocular inflammation with hypopyon, 610

Hypotony
Vitreous pulsations, relative hypotony, and retrobulbar cyst associated with a congenital optic pit (letter), 767

I

Implant
Sculpting of hydroxyapatite implants—correction (correspondence), 380

Infants
Development of object vision in infants with permanent cortical visual impairment, 575
Diode laser photocoagulation for prethreshold, posterior, retinopathy of prematurity, 589
Stereopsis after congenital monocular cataract extraction, 314

Injuries
Intraocular trauma from a microwave oven (letter), 99
Ocular injuries caused by misuse of an immersion heater (letter), 100
Vitrectomy for perforating eye injuries from shotgun pellets, 81

Intraocular lens
Intraocular lens power calculations for multifocal intraocular lenses, 405
Penetrating keratoplasty and transscleral fixation of posterior chamber lens, 182
Posterior capsulotomy as a complication of indirect laser photocoagulation, 600
Progression of nonproliferative diabetic retinopathy and visual outcome after extracapsular cataract extraction and intraocular lens implantation, 448
Racial differences in the prevalence of intraocular lens implants in the United States, 667

Intraocular pressure
Anaphylactic shock and death after oral intake of acetazolamide (letter), 367
Changes in optic disk characteristics and the number of nerve fibers in experimental glaucoma, 554
Intraocular pressure decrease in household contacts of patients with Hansen's disease and endemic control subjects, 479
Pattern discrimination perimetry in patients with glaucoma and ocular hypertension, 297
Prophylactic use of apraclonidine for intraocular pressure increase after Nd:YAG capsulotomies (correspondence), 377
Short-term effects of levobunolol on ocular pulsatile flow, 280

Iridocorneal endothelial syndrome
Progress and regression of partial corneal involvement in the iridocorneal endothelial syndrome, 171

Iridoschisis
The association of iridoschisis and angle-recession glaucoma (letter), 766

Iris
Mucogenic glaucoma caused by an epithelial cyst of the iris stroma (letter), 222
Nucleolar organizer regions in iris nevi and melanomas, 202

J

Juvenile rheumatoid arthritis
Causes of reduced visual acuity on long-term follow-up after cataract extraction in patients with uveitis and juvenile rheumatoid arthritis, 708

K

Keratectomy
Corneal sensitivity after photorefractive keratectomy, 51
Paraformaldehyde-induced keratitis after photorefractive keratectomy, 339
Photorefractive keratectomy for severe postkeratoplasty astigmatism, 429
Recurrence of herpes simplex after excimer laser keratectomy (letter), 96

Keratitis
Ciprofloxacin-resistant bacterial keratitis, 336
Fungal keratitis after radial keratotomy (letter), 369
Fungal keratitis from nylon line lawn trimmers, 437
Paraformaldehyde-induced keratitis after photorefractive keratectomy, 339
Recurrence of herpetic stromal keratitis after a conjunctival flap surgical procedure (letter), 231
Streptococcus viridans-induced crystalline keratopathy and fungal keratitis (letter), 97

Keratoconjunctivitis sicca
Keratoconjunctivitis sicca in a patient with a Jones tube to treat sleep apnea (letter), 234
Topical fibronectin in the treatment of keratoconjunctivitis sicca, 441
The use of polymerase chain reaction for the detection of chlamydial keratoconjunctivitis, 685

Keratoconus
Clinical and histopathologic changes in the host cornea after epikeratoplasty for keratoconus, 161

Keratopathy
Streptococcus viridans-induced crystalline keratopathy and fungal keratitis (letter), 97

Keratoplasty
11-0 Mersilene as running suture for penetrating keratoplasty, 675
Penetrating keratoplasty and transscleral fixation of posterior chamber lens, 182
Photorefractive keratectomy for severe postkeratoplasty astigmatism, 429

Keratotomy
Fungal keratitis after radial keratotomy (letter), 369

L

Lacrimal apparatus
Therapeutic index of epinephrine and dipivefrin with nasolacrimal occlusion, 8
Therapeutic index of pilocarpine, carbachol, and timolol with nasolacrimal occlusion, 1

Laser
Apraclonidine and argon laser trabeculoplasty, 19
Apraclonidine and argon laser trabeculoplasty (correspondence), 778
Argon laser gonioplasty in the treatment of angle-closure glaucoma, 14
Argon laser treatment of trichiasis (correspondence), 379
Corneal sensitivity after photorefractive keratectomy, 51
Diode laser photocoagulation for prethreshold, posterior, retinopathy of prematurity, 589
Histologic study of healing after ab interno laser sclerostomy, 216
The influence of exposure duration in transscleral Nd:YAG laser cyclophotocoagulation, 560
Multifunction endolaser probe (letter), 103
Multifunction endolaser probe (correspondence), 648
Posterior capsulotomy as a complication of indirect laser photocoagulation, 600
Prophylactic use of apraclonidine for intraocular pressure increase after Nd:YAG capsulotomies (correspondence), 377
Reactivation of latent herpes simplex virus by excimer laser photokeratectomy, 45
Recurrence of herpes simplex after excimer laser keratectomy (letter), 96

Lens
Aqueous dynamics in exfoliation syndrome, 473
Retained lens fragments after phacoemulsification manifesting as market intraocular inflammation with hypopyon, 610

Levobunolol
Short-term effects of levobunolol on ocular pulsatile flow, 280

Lymphoma
Visual recovery after radiation therapy of orbital lymphoma (letter), 645

M

Macula
Immunohistochemical and histochemical properties of surgically excised subretinal neovascular membranes in age-related macular degeneration, 464
Impending macular hole associated with topical pilocarpine (letter), 765
Macular phototoxicity caused by fiberoptic endoillumination during pars plana vitrectomy, 287
Prediction of visual recovery after scleral buckling of macula-off retinal detachments, 715
Retinal neovascularization and cystoid macular edema in punctate albescens retinopathy (letter), 507

Macular degeneration
Immunohistochemical and histochemical properties of surgically excised subretinal neovascular membranes in age-related macular degeneration, 464
Surgical excision of subfoveal neovascular membranes in age-related macular degeneration (correspondence), 241

Maculopathy
Hypotonous maculopathy after trabeculectomy with subconjunctival 5-fluorouracil, 544
Severe anaphylactic reaction after indocyanine green fluorescence angiography (letter), 638

Meibomian gland
Meibomian gland function and giant papillary conjunctivitis, 188

Melanoma
Nucleolar organizer regions in iris nevi and melanomas, 202

Membranoproliferative glomerulonephritis
Posterior segment changes in membranoproliferative glomerulonephritis, 593

Methamphetamine
Sudden retinal manifestations of intranasal cocaine and methamphetamine abuse, 158

Microphthalmia
Hereditary microphthalmia with colobomatous cyst, 30

Mitochondria
Ophthalmic involvement in myo-neuro-gastrointestinal encephalopathy syndrome, 322

Mitomycin C
Corneoscleral, ciliary body, and vitreoretinal toxicity after excessive instillation of mitomycin C (letter), 503

Molteno implant
Late-onset sterile endophthalmitis after Molteno tube implantation (letter), 771
Removable ligature during Molteno implant procedure (letter), 102

***Moraxella* sp.**
Moraxella infection of a scleral buckle (letter), 637

Muscle
Recession of both horizontal recti muscles in Duane's retraction syndrome with elevation and depression of the adducted eye, 311
Superior rectus muscle overaction after cataract extraction, 72
Surgical management of myokymia of the superior oblique muscle, 693
Torsional diplopia after transantral orbital decompression and extraocular muscle surgery associated with Graves' orbitopathy (correspondence), 239
Vagal responses to adjustable sutures in strabismus correction, 307

Myasthenia gravis
The edrophonium-Hess screen test in the diagnosis of ocular myasthenia gravis, 489

Mycobacterium sp.
Intraocular pressure decrease in household contacts of patients with Hansen's disease and endemic control subjects, 479

Myokymia
Surgical management of myokymia of the superior oblique muscle, 693

Myo-neuro-gastrointestinal encephalopathy syndrome
Ophthalmic involvement in myo-neuro-gastrointestinal encephalopathy syndrome, 322

Myopia
Intraocular lens power calculations for multifocal intraocular lenses, 405

N

Neovascularization
Choroidal neovascularization occurring within a demarcation line (letter), 101
Immunohistochemical and histochemical properties of surgically excised subretinal neovascular membranes in age-related macular degeneration, 464
Retinal neovascularization and cystoid macular edema in punctate albescens retinopathy (letter), 507

Nerve
Causes and prognosis in 4,278 cases of paralysis of the oculomotor, trochlear, and abducens cranial nerves (correspondence), 777

Neuropathy
Ophthalmic involvement in myo-neuro-gastrointestinal encephalopathy syndrome, 322

Nevus
Nucleolar organizer regions in iris nevi and melanomas, 202

Nocardia sp.
Nocardial scleritis (letter), 371
Preseptal cellulitis caused by *Nocardia brasiliensis* (letter), 373

Nucleolar organizer
Nucleolar organizer regions in iris nevi and melanomas, 202

Nystagmus
Behr's syndrome and 3-methylglutaconic aciduria, 494
Ocular findings in Cockayne syndrome, 579
Position-dependent Parinaud's syndrome (letter), 107
Treatment of acquired intermittent horizontal jerk nystagmus with baclofen (letter), 366

O

Obituaries
Bruce, Gordon M. 1901–1992 (JONES, I. S.), 245
Meyer-Schwickerath, G. 1920–1992 (HÖPPING, W., WAUBKE, T., and WESSING, A.), 246

Occlusion
Central retinal artery occlusion after neck irradiation (letter), 224
Sudden retinal manifestations of intranasal cocaine and methamphetamine abuse (correspondence), 780
Use of a transparent film dressing to enhance compliance with occlusion therapy for amblyopia (letter), 229

Ocular injuries
Fungal keratitis from nylon line lawn trimmers, 437
Ocular hydrofluoric acid burns, 420
Pure ocular blast injury (letter), 504

Oculomotor nerve
Acquired oculomotor, trochlear, and abducent cranial nerve palsies in pediatric patients, 568
Causes and prognosis in 4,278 cases of paralysis of the oculomotor, trochlear, and abducens cranial nerves (correspondence), 777

Optic atrophy
Behr's syndrome and 3-methylglutaconic aciduria, 494

Optic disk
Changes in optic disk characteristics and the number of nerve fibers in experimental glaucoma, 554

Optic nerve
Spontaneous retinal reattachment in a patient with persistent hyperplastic primary vitreous and an optic nerve coloboma (letter), 769

Optic neuropathy
Optic neuropathy in Hodgkin's disease, 625

Optic pit
Vitreous pulsations, relative hypotony, and retrobulbar cyst associated with a congenital optic pit (letter), 767

Orbit
Contralateral occipital depression related to obstetric forceps injury to the eye, 318
Inflammatory oribital tumor as an ocular sign of a battered child (letter), 510
Orbital cellulitis caused by *Eikenella corrodens*, 584
Sculpting of hydroxyapatite implants—correction (correspondence), 380
Torsional diplopia after transantral orbital decompression and extraocular muscle surgery associated with Graves' orbitopathy (correspondence), 239
Visual recovery after radiation therapy of orbital lymphoma (letter), 645

Oxygen
Adjunctive hyperbaric oxygen in the treatment of bilateral cerebro-rhino-orbital mucormycosis, 208

P

Palsy
Acquired oculomotor, trochlear, and abducent cranial nerve palsies in pediatric patients, 568
Paroxysmal eyelid retractions (letter), 105

Parinaud's syndrome
Position-dependent Parinaud's syndrome (letter), 107

Pemphigus
Conjunctival involvement in paraneoplastic pemphigus, 621

Penetrating keratoplasty
Running nylon suture dissolution after penetrating keratoplasty (correspondence), 240
Visual outcome after penetrating keratoplasty with double continuous or combined interrupted and continuous suture wound closure, 63

Perimetry
Long-term and short-term fluctuation in pattern discrimination perimetry, 302
Pattern discrimination perimetry in patients with glaucoma and ocular hypertension, 297

Perspectives
Acquired immunodeficiency syndrome and ophthalmology: the first decade, 86
Controversies in the management of retinopathy of prematurity (correspondence), 237
The development of new drugs for ophthalmology, 357
Neuro-ophthalmic associations and complications of diabetes mellitus, 498

Phacoemulsification
Retained lens fragments after phacoemulsification manifesting as market intraocular inflammation with hypopyon, 610

Photocoagulation
Diode laser photocoagulation for prethreshold, posterior, retinopathy of prematurity, 589
Posterior capsulotomy as a complication of indirect laser photocoagulation, 600

Photokeratectomy
Reactivation of latent herpes simplex virus by excimer laser photokeratectomy, 45

Pigment dispersion syndrome
Lattice degeneration of the retina and the pigment dispersion syndrome, 539

Pilocarpine
Impending macular hole associated with topical pilocarpine (letter), 765
Therapeutic index of pilocarpine, carbachol, and timolol with nasolacrimal occlusion, 1

Posterior segment
Posterior segment changes in membranoproliferative glomerulonephritis, 593

Potential Acuity Meter
Use of the potential acuity meter in suspected functional visual loss (letter), 502

Proliferative vitreoretinopathy
Pathogenetic mechanisms in anterior proliferative vitreoretinopathy, 257

***Proteus* sp.**
Six cases of scleritis associated with systemic infection, 55

Pterygium
Corneoscleral, ciliary body, and vitreoretinal toxicity after excessive instillation of mitomycin C (letter), 503

Pupil
Idiopathic alternating anisocoria (letter), 509
Position-dependent Parinaud's syndrome (letter), 107
Stray light in radial keratotomy and the influence of pupil size and straylight angle, 424

R

Radial keratotomy
Stray light in radial keratotomy and the influence of pupil size and straylight angle, 424

Radiation
Central retinal artery occlusion after neck irradiation (letter), 224
Malignant myoepithelioma after radiation for retinoblastoma (letter), 512
Visual recovery after radiation therapy of orbital lymphoma (letter), 645

Retina
Bilateral radiant damage to the cornea and retina after exposure to a 700-V electric discharge (letter), 775
Central retinal artery occlusion after neck irradiation (letter), 224
Development of a retinal artery macroaneurysm at the site of a previously detected retinal artery embolus (letter), 642
Efficacy of fluid-air exchange for postvitrectomy diabetic vitreous hemorrhage, 457
Frosted branch angiitis associated with cytomegalovirus retinitis (correspondence), 514
Immunohistochemical and histochemical properties of surgically excised subretinal neovascular membranes in age-related macular degeneration, 464
In situ detection of human herpesvirus 6 in retinitis associated with acquired immunodeficiency syndrome (letter), 375
Lattice degeneration of the retina and the pigment dispersion syndrome, 539
Mild frosted branch periphlebitis (letter), 505
Multifunction endolaser probe (letter), 103
Ocular findings in Cockayne syndrome, 579
Pathogenetic mechanisms in anterior proliferative vitreoretinopathy, 257
Polymerase chain reaction for the detection of the Varicella-zoster genome in ocular samples from patients with acute retinal necrosis, 603
Retinal neovascularization and cystoid macular edema in punctate albescens retinopathy (letter), 507
Subretinal diathermy probe (letter), 508
Sudden retinal manifestations of intranasal cocaine and methamphetamine abuse, 158

Sudden retinal manifestations of intranasal cocaine and methamphetamine abuse (correspondence), 780

X-Linked recessive familial exudative vitreoretinopathy, 145

Retinal detachment
Impending macular hole associated with topical pilocarpine (letter), 765

Intraconjunctival cavitary inclusions of silicone oil complicating retinal detachment repair (letter), 639

Lattice degeneration of the retina and the pigment dispersion syndrome, 539

Moraxella infection of a scleral buckle (letter), 637

Multifunction endolaser probe (letter), 103

Pathogenetic mechanisms in anterior proliferative vitreoretinopathy, 257

Prediction of visual recovery after scleral buckling of macula-off retinal detachments, 715

Spontaneous retinal reattachment in a patient with persistent hyperplastic primary vitreous and an optic nerve coloboma (letter), 769

Retinitis pigmentosa
Ultrastructural findings in an autopsy eye from a patient with Usher's syndrome type II, 748

Retinoblastoma
Calcified intraocular abscess simulating retinoblastoma (letter), 227

Malignant myoepithelioma after radiation for retinoblastoma (letter), 512

Successful therapy for trilateral retinoblastoma, 23

Successful therapy for trilateral retinoblastoma (correspondence), 646

Successful therapy for trilateral retinoblastoma (correspondence), 647

Retinopathy
Retinal neovascularization and cystoid macular edema in punctate albescens retinopathy (letter), 507

Retinopathy of prematurity
Controversies in the management of retinopathy of prematurity (correspondence), 237

Diode laser photocoagulation for prethreshold, posterior, retinopathy of prematurity, 589

S

Sclera
Moraxella infection of a scleral buckle (letter), 637

Scleritis
Nocardial scleritis (letter), 371

Six cases of scleritis associated with systemic infection, 55

Sporothrix schenckii scleritis (letter), 370

Sclerostomy
Histologic study of healing after ab interno laser sclerostomy, 216

Silicone oil
Intraconjunctival cavitary inclusions of silicone oil complicating retinal detachment repair (letter), 639

Sleep apnea
Keratoconjunctivitis sicca in a patient with a Jones tube to treat sleep apnea (letter), 234

***Sporothrix* sp.**
Sporothrix schenckii scleritis (letter), 370

Stereopsis
Stereopsis after congenital monocular cataract extraction, 314

Strabismus
Ocular findings in Cockayne syndrome, 579

Propofol and surgical contamination in strabismus surgery (letter), 635

Vagal responses to adjustable sutures in strabismus correction, 307

***Streptococcus* sp.**
Streptococcus viridans-induced crystalline keratopathy and fungal keratitis (letter), 97

Suture
11-0 Mersilene as running suture for penetrating keratoplasty, 675

Removable ligature during Molteno implant procedure (letter), 102

Running nylon suture dissolution after penetrating keratoplasty (correspondence), 240

Vagal responses to adjustable sutures in strabismus correction, 307

Visual outcome after penetrating keratoplasty with double continuous or combined interrupted and continuous suture wound closure, 63

Sweet's syndrome
Ocular complications in Sweet's syndrome (letter), 230

T

T cell
Uveitis associated with human T-cell lymphotropic virus Type I, 123

Tarsorrhaphy
Lateral tarsorrhaphy for a noncompliant patient with floppy eyelid syndrome (letter), 367

Localized distichiasis after tarsorrhaphy (letter), 104

Timolol
Therapeutic index of pilocarpine, carbachol, and timolol with nasolacrimal occlusion, 1

Toxoplasmosis
Ocular toxoplasmosis in human immunodeficiency virus-infected patients, 130

An unusually high prevalence of ocular toxoplasmosis in Southern Brazil, 136

Trabeculectomy
Closure of fornix-based posttrabeculectomy conjunctival wound leaks with autologous fibrin glue (letter), 221
Hypotonous maculopathy after trabeculectomy with subconjunctival 5-fluorouracil, 544
Results of intraoperative 5-fluorouracil supplementation on trabeculectomy for open-angle glaucoma, 737
Trabeculectomy without conjunctival incision (correspondence), 108

Trabeculoplasty
Apraclonidine and argon laser trabeculoplasty, 19
Apraclonidine and argon laser trabeculoplasty (correspondence), 778

Trichiasis
Argon laser treatment of trichiasis (correspondence), 379

Trochlear nerve
Acquired oculomotor, trochlear, and abducent cranial nerve palsies in pediatric patients, 568
Causes and prognosis in 4,278 cases of paralysis of the oculomotor, trochlear, and abducens cranial nerves (correspondence), 777

Tumor
Inflammatory oribital tumor as an ocular sign of a battered child (letter), 510
Malignant myoepithelioma after radiation for retinoblastoma (letter), 512
Successful therapy for trilateral retinoblastoma, 23

U

Ulcer
Community care of corneal ulcers, 531

Usher's syndrome
Ultrastructural findings in an autopsy eye from a patient with Usher's syndrome type II, 748

Uvea
Vogt-Koyanagi-Harada syndrome in patients with Cherokee indian ancestry, 615

Uveitis
Bilateral panuveitis, sebopsoriasis, and secondary syphilis in a patient with acquired immunodeficiency syndrome (letter), 773
Brucellosis and uveitis (letter), 374
Causes of reduced visual acuity on long-term follow-up after cataract extraction in patients with uveitis and juvenile rheumatoid arthritis, 708
Uveitis associated with human T-cell lymphotropic virus Type I, 123

V

Varicella-zoster
Central retinal artery occlusion after varicella; correction, 235
Polymerase chain reaction for the detection of the Varicella-zoster genome in ocular samples from patients with acute retinal necrosis, 603

Virus
Uveitis associated with human T-cell lymphotropic virus Type I, 123

Vision
The Tokyo metropolitan home vision screening program for amblyopia in 3-year-old children, 416

Visual acuity
Causes of reduced visual acuity on long-term follow-up after cataract extraction in patients with uveitis and juvenile rheumatoid arthritis, 708
Use of the potential acuity meter in suspected functional visual loss (letter), 502

Visual field
Visual field defects in patients with normal-tension glaucoma and patients with high-tension glaucoma, 758

Visual impairment
Development of object vision in infants with permanent cortical visual impairment, 575

Vitrectomy
Efficacy of fluid-air exchange for postvitrectomy diabetic vitreous hemorrhage, 457
Intraocular fluid cultures after primary pars plana vitrectomy, 697
Macular phototoxicity caused by fiberoptic endoillumination during pars plana vitrectomy, 287
Vitrectomy for perforating eye injuries from shotgun pellets, 81

Vitreoretinopathy
X-Linked recessive familial exudative vitreoretinopathy, 145

Vitreous
Cytokines in the vitreous of patients with proliferative diabetic retinopathy, 731
Efficacy of fluid-air exchange for postvitrectomy diabetic vitreous hemorrhage, 457
Pathogenetic mechanisms in anterior proliferative vitreoretinopathy, 257
Spontaneous retinal reattachment in a patient with persistent hyperplastic primary vitreous and an optic nerve coloboma (letter), 769
Vitreous pulsations, relative hypotony, and retrobulbar cyst associated with a congenital optic pit (letter), 767
X-Linked recessive familial exudative vitreoretinopathy, 145

Vogt-Koyanagi-Harada syndrome
Vogt-Koyanagi-Harada syndrome in patients with Cherokee indian ancestry, 615

X

***Xanthomonas* sp.**
Xanthomonas maltophilia endophthalmitis after implantation of sustained-release ganciclovir (letter), 772

AUTHOR INDEX

A

AABERG, T. M.: See GROSSNIKLAUS, H. E., 464

AABERG, T. M.: See LAMBERT, H. M., 242

AABERG, T. M.: See LOPEZ, P. F., 101, 257

AABERG, T. M.: See MARTINEZ, J. A., 615

AABERG, T. M.: See STERNBERG, P., JR., 238

ABELAIRAS, J.: See PERALTA, J., 367

ABRAMS, G. W.: See MICHELS, M., 287

ABRAMSON, D. H.: Successful therapy for trilateral retinoblastoma (correspondence), 647

ABU EL ASRAR, A. M., MAIMONE, D., MORSE, P. H., GREGORY, S., and REDER, A. T.: Cytokines in the vitreous of patients with proliferative diabetic retinopathy, 731

ADAMIAN, M.: See BERSON, E. L., 748

ADAMIS, A. P.: See KOWAL, V. O., 640

AGUT, H.: See REUX, L, 375

AIELLO, A.: See McDONNELL, P. J., 531

ALBERT, D. L., BROWNSTEIN, S., and KATTLEMAN, B. S.: Mucogenic glaucoma caused by an epithelial cyst of the iris stroma (letter), 222

ALBERT, D. M.: See KOWAL, V. O., 640

ALBERT, D. M.: See MARCUS, D. M., 202

ALFARO, D. V., TRAN, V. T., RUNYAN, T., CHONG, L. P., RYAN, S. J., and LIGGETT, P. E.: Vitrectomy for perforating eye injuries from shotgun pellets, 81

ALFONSO, E.: See MASKIN, S. L., 369

ALLEE, S.: See MAURILLO, J. A., JR., 780

ANDRES, C. W.: See HOLLAND, E. J., 680

APPLING, W. D.: See DE LA PAZ, M. A., 208

ARAKI, S.: See MOCHIZUKI, M., 123

AREND, O.: See WOLF, S., 638

ARENTSEN, J. J.: See RUBINFELD, R. S., 420

ASSIL, K. K., ZARNEGAR, S. R., and SCHANZLIN, D. J.: Visual outcome after penetrating keratoplasty with double continuous or combined interrupted and continuous suture wound closure, 63

B

BAKER, R. H.: See GHARAGOZLOO, N. Z., 473

BAKER, W. H.: See EVANS, L. S., 224

BARNES, C.: See SHAMI, M., 769

BARRON, B. A.: See CLINCH, T. E., 437

BARTLEY, G. B., and LOWRY, J. C.: Reply to GOSSMAN, M. D., YUNG, R., BERLIN, A. J., BRIGHTWELL, J. R., and WILLIAMS, J. W.: Argon laser treatment of trichiasis (correspondence), 380

BARTLEY, G. B.: See GARRITY, J. A., 240

BASTI, S.: See GUPTA, S., 503

BAUTISTA, D. V., and KEECH, R. V.: Propofol and surgical contamination in strabismus surgery (letter), 635

BEIRAN, I., and MILLER, B.: Pure ocular blast injury (letter), 504

BELFORT R., JR.: See GLASNER, P. D., 136

BELLOWS, A. R.: See WEISS, H. S., 14

BELONGIA, E. A.: See HOLLAND, E. J., 680

BEN-EZRA, D.: See SHEFFER, R. N., 494

BENEDICT, W.: See SHAMI, M., 769

BENEDICT, W. L., and SHAMI, M.: Impending macular hole associated with topical pilocarpine (letter), 765

BENNER, J. D.: See COHEN, S. M., 697

BENSINGER, R.: Atlas of Ophthalmic Surgery, volume II, Oculoplastic, Lacrimal, and Orbital Surgery, by Dutton, J. J. (book review), 651

BENSON, W.: See WALLACE, R. T., 158

BERLIN, A. J.: See GOSSMAN, M. D., 379

BERSON, E. L., and ADAMIAN, M.: Ultrastructural findings in an autopsy eye from a patient with Usher's syndrome type II, 748

BEZZINA, A. M.: Ultrasound biomicroscopy of anterior segment structures in normal and glaucomatous eyes (correspondence), 516

BILLBOROUGH, M.: See MATHERS, W. D., 188

BISWELL, R.: See SHERMAN, M. D., 233

BORCHERT, M.: See ROSMONDO, V., 107

BOSEM, M. E., LUSKY, M., and WEINREB, R. N.: Short-term effects of levobunolol on ocular pulsatile flow, 280

BOUCHARD, C. S.: Lateral tarsorrhaphy for a noncompliant patient with floppy eyelid syndrome (letter), 367

BOURNE, W. M., and BRUBAKER, R. F.: Progress and regression of partial corneal involvement in the iridocorneal endothelial syndrome, 171

BRIGHT, R. A.: See SHARKNESS, C. M., 667

BRIGHTWELL, J. R.: See GOSSMAN, M. D., 379

BRINT, S. F.: See SILVERSTONE, D. E., 378

BRODSKY, M. C., SHARP, G. B., FRITZ, K. J., and CORBETT, J. J.: Idiopathic alternating anisocoria (letter), 509

BRODSTEIN, D. E.: See HOLMWOOD, P. C., 19, 778

BROOKS, J. G., JR., MILLS, R. A. D., and COSTER, D. J.: Nocardial scleritis (letter), 371

BROWN, G. C.: See WALLACE, R. T., 158

BROWN, S. I.: See FRUEH, B. E., 240, 675

BROWN, V. B.: See GROSSNIKLAUS, H. E., 464

BROWNING, D. J.: Mild frosted branch periphlebitis (letter), 505
BROWNSTEIN, S.: See ALBERT, D. L., 222
BRUBAKER, R. F.: See BOURNE, W. M., 171
BRUBAKER, R. F.: See GHARAGOZLOO, N. Z., 473
BRUNETTE, I., and STULTING, R. D.: *Sporothrix schenckii* scleritis (letter), 370
BUCKLEY, E. G.: See NELSON, S. C., 23, 647, 648
BUETTNER, H.: See YAP, E.-Y., 225
BURDE, R. M.: Neuro-ophthalmic associations and complications of diabetes mellitus, 498
BURGESS, S. K.: See McDONALD, M. B., 318
BURK, L. L.: See SILVERSTONE, D. E., 378
BURNIER, M., JR.: See GLASNER, P. D., 136
BURRIS, T. E.: See LINDSTROM, R. L., 345
BURTON, T. C.: See JAFFE, G. J., 448
BYRNE, S. F.: See SIATKOWSKI, R. M., 625

C

CALLANAN, D., and RUBSAMEN, P. E.: *Moraxella* infection of a scleral buckle (letter), 637
CAMARGO, M. E.: See GLASNER, P. D., 136
CAMISA, C.: See MEYERS, S. J., 621
CAMPOS, M., HERTZOG, L., GARBUS, J. J., and McDONNELL, P. J.: Corneal sensitivity after photorefractive keratectomy, 51
CAMPOS, M., HERTZOG, L., GARBUS, J. J., LEE, M., and McDONNELL, P. J.: Photorefractive keratectomy for severe postkeratoplasty astigmatism, 429
CAPONE, A.: See STERNBERG, P., JR., 238
CAPONE, A., JR.: See GROSSNIKLAUS, H. E., 464
CAPONE, A., JR.: See LAMBERT, H. M., 242
CAPONE, A., JR.: See LOPEZ, P. F., 101
CAPONE, A., JR.: See LOPEZ, P. F., 257
CAPONE, A., JR.: See MARTINEZ, J. A., 615
CARDOZO, O. L.: See VERAART, H. G. N., 424
CARTWRIGHT, M. J.: Sculpting of hydroxyapatite implants—correction (correspondence), 380
CARTWRIGHT, M. J., and FRUEH, B. R.: Keratoconjunctivitis sicca in a patient with a Jones tube to treat sleep apnea (letter), 234
CATALANO, R. A.: See CHEN, T. C., 575
CEVALLOS, V.: See SHERMAN, M. D., 233
CHAFFIN, D.: Ocular Emergencies, by Catalano, R. A. (book review), 650
CHAIWAT, T.: See RITCH, R., 484
CHANG, C.-J.: See CHEN, M.-S., 723
CHANG, S.: Multifunction endolaser probe (correspondence), 648
CHANSUE, E.: See PEPOSE, J. S., 45
CHARLES, S. T.: See FLEMING, T. N., 589
CHASE, D. S.: See VRABEC, M. P., 96
CHASE, R. D.: See HOLMWOOD, P. C., 19, 778
CHEN, C.-J.: See CHEN, M.-S., 723
CHEN, M.-S., KAO, C.-S., CHANG, C.-J., WU, T.-J., FU, C.-C., CHEN, C.-J., and TAI, T.-Y.: Prevalence and risk factors of diabetic retinopathy among noninsulin-dependent diabetic subjects, 723
CHEN, S., STROH, E. M., WALD, K., and JALKH, A.: *Xanthomonas maltophilia* endophthalmitis after implantation of sustained-release ganciclovir (letter), 772
CHEN, T. C., WEINBERG, M. H., CATALANO, R. A., SIMON, J. W., and WAGLE, W. A.: Development of object vision in infants with permanent cortical visual impairment, 575
CHIANG, T.: See HUSSEIN, N., 479
CHIPONT, E.: See DÍAZ-LLOPIS, M., 742
CHIRON KERATOCONJUNCTIVITIS SICCA STUDY GROUP: See NELSON, J. D., 441
CHO, N.-C., and HAN, H.-J.: Central retinal artery occlusion after varicella; correction, 235
CHOE, W.: See MOSHFEGHI, D. M., 645
CHONG, L. P.: See ALFARO, D. V., 81
CHOPRA, H.: See HOLMWOOD, P. C., 19, 778
CHRISTENSEN, L. E.: See WRIGHT, K. W., 409
CHU, W.: Current Practice in Ophthalmology, by Schacht, A. P. (ed.) (book review), 784
CLINCH, T. E., ROBINSON, M. J., BARRON, B. A., INSLER, M. S., LIANG, K., and KAUFMAN, H. E.: Fungal keratitis from nylon line lawn trimmers, 437
CLORFEINE, G. S., and PARKER, W. T.: Use of a transparent film dressing to enhance compliance with occlusion therapy for amblyopia (letter), 229
COCHEREAU-MASSIN I., LEHOANG, P., LAUTIER-FRAU, M., ZERDOUN, E., ZAZOUN, L., ROBINET, M., MARCEL, P., GIRARD, B., KATLAMA, C., LEPORT, C., ROZENBAUM, W., COULAUD, J. P., and GENTILINI, M.: Ocular toxoplasmosis in human immunodeficiency virus-infected patients, 130
COHEN, K. L.: See LISCH, W., 35
COHEN, R. B.: See MOSHFEGHI, D. M., 645
COHEN, S.: Fluorescein Angiography. Technique, Interpretation, and Application, by Nanjiani, M. (book review), 382
COHEN, S. M., BENNER, J. D., LANDERS, M. B., III, and MORSE, L. S.: Intraocular fluid cultures after primary pars plana vitrectomy, 697
COLL, G. E., and DEMER, J. L.: The edrophonium-Hess screen test in the diagnosis of ocular myasthenia gravis, 489
CORBETT, J. J.: See BRODSKY, M. C., 509
CORDER, D. M.: See ZEITER, J. H., 780
COSTER, D. J.: See BROOKS, J. G., JR., 371
COULAUD, J. P.: See COCHEREAU-MASSIN I., 130
CULBERTSON, W.: See FOX, G. M., 708

CUNNINGHAM, R. D.: The Lazy Eye. A Simulation Environment for Neuro-Ophthalmology. Computer Software, by Bregman, H. S., Ly, P. T., and Galetta, S. (book review), 651

D

DAVIS, J. L.: See FOX, G. M., 708
DAVIS, R. M.: See LINDSTROM, R. L., 345
DAYA, S. M.: See HOLLAND, E. J., 182
DE BECKER, I.: See TRABOULSI, E. I., 579
DEFALLER, J. M.: See SILVERSTONE, D. E., 378
DE LA MAZA, M. S.: See HEMADY, R., 55
DE LA PAZ, M. A., PATRINELY, J. R., MARINES, H. M., and APPLING, W. D.: Adjunctive hyperbaric oxygen in the treatment of bilateral cerebro-rhino-orbital mucormycosis, 208
DEMATTEO, M. P., and VRABEC, M. P.: Intraocular trauma from a microwave oven (letter), 99
DEMER, J. L.: See COLL, G. E., 489
DE POTTER, P.: See SHIELDS, J. A., 227
DE SA, L. C., GOOD, W. V., and HOYT, C. S.: Surgical management of myokymia of the superior oblique muscle, 693
DÍAZ-LLOPIS, M., CHIPONT, E., SANCHEZ, S., ESPAÑA, E., NAVEA, A., and MENEZO, J. L.: Intravitreal foscarnet for cytomegalovirus retinitis in a patient with acquired immunodeficiency syndrome, 742
DIPAOLO, F.: See PILLAI, S, 773
DOLPHIN, K., and LINCOFF, H.: Bilateral radiant damage to the cornea and retina after exposure to a 700-V electric discharge (letter), 775
DONAHUE, S. P., FRIBERG, T. R., and JOHNSON, B. L.: Intraconjunctival cavitary inclusions of silicone oil complicating retinal detachment repair (letter), 639
DOUGHMAN, D. J.: See HOLLAND, E. J., 182
DOUGLAS, C. H.: See SHIELDS, J. A., 227
DOYLE, J. W.: See SMITH, M. F., 737
DRIEBE, W.: See KAUFMANN, J. G., 97
DURRIE, D. S.: See VRABEC, M. P., 96
DYER, J. A.: See GARRITY, J. A., 240

E

EAGLE, R. C.: See SHIELDS, J. A., 227
ECHELMAN, D. A.: See PRUM, B. E., 560
EDELHAUSER, H. F.: See KIM, E. K., 329
EGAN, K. M.: See MARCUS, D. M., 202
EGBERT, P. R.: See SHAHINIAN, L., JR., 216
EHSAN, Q.: See HUSSEIN, N., 479
EISWIRTH, C. C.: See EUSTIS, H. S., 307
ELLER, A. W.: See FRIBERG, T. R., 715
ELLIS, F. D.: See PLAGER, D. A., 145
ELPELEG, O. N.: See SHEFFER, R. N., 494
EMMIG, C.-T.: See LISCH, W., 35
ENZENAUER, R. W.: See WATERHOUSE, W., 510
ENZER, Y. R.: See SHORR, N., 779
ESPAÑA, E.: See DÍAZ-LLOPIS, M., 742
EUSTIS, H. S., EISWIRTH, C. C., and SMITH, D. R.: Vagal responses to adjustable sutures in strabismus correction, 307
EVANGELISTA, A.: See HOLLAND, E. J., 182
EVANS, L. S., VAN DE GRAAFF, W. B., BAKER, W. H., and TRIMBLE, S. N.: Central retinal artery occlusion after neck irradiation (letter), 224

F

FATOURECHI, V.: See GARRITY, J. A., 240
FELDMAN, R. M.: See FRUEH, B. E., 240
FELDMAN, R. M.: See LEVI, L., 502
FELDMAN, S. T.: See FRUEH, B. E., 240, 675
FERNÁNDEZ-GUARDIOLA, J.: See PERALTA, J., 367
FERRELL, R. E.: See MINTZ-HITTNER, H. A., 700
FILLET, A.-M.: See REUX, I., 375
FINGER, P. T.: See MOSHFEGHI, D. M., 645
FLEENER, C. H.: See HUNTER, L. R., 373
FLEMING, T. N., RUNGE, P. E., and CHARLES, S. T.: Diode laser photocoagulation for prethreshold, posterior, retinopathy of prematurity, 589
FLETCHER, D. C.: See SABATES, F. N., 241
FLYNN, H. W., JR.: See FOX, G. M., 708
FLYNN, H. W., JR.: See IRVINE, W. D., 610
FOLBERG, R.: Ocular Pathology. A Color Atlas, ed. 2, by Myron, Y., and Fine, B. S. (book review), 782
FOSTER, C. S.: See HEMADY, R., 55
FOSTER, F. S.: See PAVLIN, C. J., 517
FOX, G. M., FLYNN, H. W., JR., DAVIS, J. L., and CULBERTSON, W.: Causes of reduced visual acuity on long-term follow-up after cataract extraction in patients with uveitis and juvenile rheumatoid arthritis, 708
FRIBERG, T. R., and ELLER, A. W.: Prediction of visual recovery after scleral buckling of macula-off retinal detachments, 715
FRIBERG, T. R., and MCLELLAN, T. G.: Vitreous pulsations, relative hypotony, and retrobulbar cyst associated with a congenital optic pit (letter), 767
FRIBERG, T. R.: See DONAHUE, S. P., 639
FRIEDMAN, H. S.: See NELSON, S. C., 23, 647, 648
FRIENDLY, D. S.: See MILLER, B. A., 366
FRITZ, K. J.: See BRODSKY, M. C., 509
FRUCHT-PERY, J.: See FRUEH, B. E., 240
FRUEH, B. E., BROWN, S. I., and FELDMAN, S. T.: 11-0 Mersilene as running suture for penetrating keratoplasty, 675
FRUEH, B. E., FELDMAN, S. T., FELDMAN, R. M., SOSSI, N. P., BROWN, S. I., and FRUCHT-PERY, J.: Reply to LAM, S., and TESSLER, H. H.: Running nylon suture dissolution after penetrating keratoplasty (correspondence), 240
FRUEH, B. R.: See CARTWRIGHT, M. J., 234
FU, C.-C.: See CHEN, M.-S., 723

FULLER, G. N.: See NELSON, S. C., 23, 647, 648
FUNDERBURGH, J.: See RODRIGUES, M., 161
FUQUA, M.: See ZIMMERMAN, T. J., 1, 8

G

GANS, L. A.: See PEPOSE, J. S., 45
GARBUS, J. J.: See CAMPOS, M., 429
GARBUS, J. J.: See CAMPOS, M., 51
GARCIA-FERRER, F.: See TALLEY, A. R., 685
GARRITY, J. A., SAGGAU, D. D., GORMAN, C. A., BARTLEY, G. B., FATOURECHI, V., HARDWIG, P. W., and DYER, J. A.: Reply to KUSHNER, B. J.: Torsional diplopia after transantral orbital decompression and extraocular muscle surgery associated with Graves' orbitopathy (correspondence), 240
GAUDERMAN, W. J.: See McDONNELL, P. J., 531
GEIER, S. A., NASEMANN, J., KLAUSS, V., KRONA-WITTER, U., and GOEBEL, F. D.: Frosted branch angiitis associated with cytomegalovirus retinitis (correspondence), 514
GENTILINI, M.: See COCHEREAU-MASSIN I., 130
GEROSKI, D. H.: See KIM, E. K., 329
GERSHONI-BARUCH, R.: See PORGES, Y., 30
GHARAGOZLOO, N. Z., BAKER, R. H., and BRUBAKER, R. F.: Aqueous dynamics in exfoliation syndrome, 473
GIRARD, B.: See COCHEREAU-MASSIN I., 130
GLASER, J. S.: See SIATKOWSKI, R. M., 625
GLASNER, P. D., SILVEIRA, C., KRUSZON-MORAN, D., MARTINS, M. C., BURNIER, M., JR., SILVEIRA, S., CAMARGO, M. E., NUSSENBLATT, R. B., KASLOW, R. A., and BELFORT R., JR.: An unusually high prevalence of ocular toxoplasmosis in Southern Brazil, 136
GOEBEL, F. D.: See GEIER, S. A., 514
GOLDENFELD, M.: See HOLMWOOD, P. C., 19, 778
GOLDGERG, I.: See GRAHAM, S. L., 221
GOLDSCHER, D.: See PORGES, Y., 30
GOLES, K. G.: See PALLIKARIS, I. G., 339
GOLNIK, K. C.: See THRELKELD, A. B., 322
GOOD, W. V.: See DE SA, L. C., 693
GOODE, S. M.: See KOONER, K. S., 102
GOODE, S. M.: See WEISS, H. S., 14
GOODMAN, J. L.: See HOLLAND, E. J., 680
GORDON, J. F.: See LINDSTROM, R. L., 345
GORDON, J. F.: See NELSON, J. D., 441
GORMAN, C. A.: See GARRITY, J. A., 240
GOSSMAN, M. D., YUNG, R., BERLIN, A. J., BRIGHTWELL, J. R., and WILLIAMS, J. W.: Argon laser treatment of trichiasis (correspondence), 379
GRAHAM, S. L., MURRAY, B., and GOLDGERG, I.: Closure of fornix-based posttrabeculectomy conjunctival wound leaks with autologous fibrin glue (letter), 221
GREENBAUM, S.: Parabulbar anesthesia (letter), 776
GREGG, F. M., and PARKS, M. M.: Stereopsis after congenital monocular cataract extraction, 314
GREGORY, S.: See ABU EL ASRAR, A. M., 731
GRIFFIN, J. W.: See THRELKELD, A. B., 322
GRIMMETT, M. R., and LAMBERT, S. R.: Superior rectus muscle overaction after cataract extraction, 72
GROOS, E.: The Surgical Rehabilitation of Vision, by Nordon, L. T., Maxwell, W. A., and Davison, J. A. (eds.) (book review), 518
GROSSNIKLAUS, H. E., MARTINEZ, J. A., BROWN, V. B., LAMBERT, H. M., STERNBERG, P., JR., CAPONE, A., JR., AABERG, T. M., and LOPEZ, P. F.: Immunohistochemical and histochemical properties of surgically excised subretinal neovascular membranes in age-related macular degeneration, 464
GROSSNIKLAUS, H. E.: See LOPEZ, P. F., 257
GROSSNIKLAUS, H. E.: See SAXE, S. J., 512
GUPTA, S., and BASTI, S.: Corneoscleral, ciliary body, and vitreoretinal toxicity after excessive instillation of mitomycin C (letter), 503
GUTMAN, J.: The Eye in General Practice, ed. 9, by Jackson, C. R. S., and Finlay, R. D. (book review), 383
GUYTON, D. L.: Optics and Refraction. A User-Friendly Guide., by Miller, D. (book review), 650

H

HALLER, J. A.: See HEHER, K. L., 771
HALPERIN, E. C.: See NELSON, S. C., 23, 647, 648
HAMBURGER, S.: See SHARKNESS, C. M., 667
HAMILTON, P. M.: See SHARKNESS, C. M., 667
HAN, D. P.: See MICHELS, M., 287
HAN, H.-J.: See CHO, N.-C. 235
HANASHIRO, R.: See NISHI, M., 603
HARASIEWICZ, K.: See PAVLIN, C. J., 517
HARBIN, T. S., JR.: See RITCH, R., 484
HARDWIG, P. W.: See GARRITY, J. A., 240
HARTZ, A.: See JAFFE, G. J., 448
HARTZER, M.: See PLAGER, D. A., 145
HAUW, J.-J.: See REUX, I., 375
HEHER, K. L., LIM, J. I., HALLER, J. A., and JAMPEL, H. D.: Late-onset sterile endophthalmitis after Molteno tube implantation (letter), 771
HEMADY, R., DE LA MAZA, M. S., RAIZMAN, M. B., and FOSTER, C. S.: Six cases of scleritis associated with systemic infection, 55
HEMADY, R., ZIMMERMAN, A., KATZEN, B. W., and KARESH, J. W.: Orbital cellulitis caused by *Eikenella corrodens*, 584
HERTZOG, L.: See CAMPOS, M., 51, 429
HINDLE, N. W.: Controversies in the management of retinopathy of prematurity (correspondence), 237
HIROKAWA, K.: See LINDSTROM, R. L., 345

HOCKENBERGER, B.: See NELSON, S. C., 23, 647, 648

HOFFER, K. J.: See HOLLADAY, J. T., 405

HOLLADAY, J. T., and HOFFER, K. J.: Intraocular lens power calculations for multifocal intraocular lenses, 405

HOLLAND, E. J., DAYA, S. M., EVANGELISTA, A., KETCHAM, J. M., LUBNIEWSKI, A. J., DOUGHMAN, D. J., and LANE, S. S.: Penetrating keratoplasty and transscleral fixation of posterior chamber lens, 182

HOLLAND, E. J., MAHANTI, R. L., BELONGIA, E. A., MIZENER, M. W., GOODMAN, J. L., ANDRES, C. W., and OSTERHOLM, M. T.: Ocular involvement in an outbreak of herpes gladiatorum, 680

HOLLAND, G. N.: Acquired immunodeficiency syndrome and ophthalmology: the first decade, 86

HOLLEY, G. P.: See KIM, E. K., 329

HOLMWOOD, P. C., CHASE, R. D., KRUPIN, T., ROSENBERG, L. F., RUDERMAN, J. M., TALLMAN, B. A., BRODSTEIN, D. E., CHOPRA, H., and GOLDENFELD, M.: Apraclonidine and argon laser trabeculoplasty, 19

HOLMWOOD, P. C., CHASE, R. D., KRUPIN, T., ROSENBERG, L. F., RUDERMAN, J. M., TALLMAN, B. A., BRODSTEIN, D. E., CHOPRA, H., and GOLDENFELD, M.: Reply to OFNER, S., SAMPLES, J. R., and VAN BUSKIRK, E. M.: Apraclonidine and argon laser trabeculoplasty (correspondence), 778

HOLZMAN, A. E.: See JOHNSON, B. L., 633

HONDO, R.: See NISHI, M., 603

HÖPPING, W., WAUBKE, T., and WESSING, A.: Meyer-Schwickerath, G. 1920–1992 (obituary), 246

HOYT, C. S.: See DE SA, L. C., 693

HUGHES, J. R.: See SIATKOWSKI, R. M., 625

HUNT, H. H.: See NUTAITIS, M. J., 297

HUNT, H. H.: See STEWART, W. C., 302

HUNTER, L. R., KRINSKY, A. H., and FLEENER, C. H.: Preseptal cellulitis caused by *Nocardia brasiliensis* (letter), 373

HURKO, O.: See THRELKELD, A. B., 322

HUSAIN, D.: See LAKHANPAL, V., 600

HUSSAIN, R.: See HUSSEIN, N., 479

HUSSEIN, N., CHIANG, T., EHSAN, Q., and HUSSAIN, R.: Intraocular pressure decrease in household contacts of patients with Hansen's disease and endemic control subjects, 479

I

IJSPEERT, J. K.: See VERAART, H. G. N., 424

INSLER, M. S.: See CLINCH, T. E., 437

IRVINE, W. D., FLYNN, H. W., JR., MURRAY, T. G., and RUBSAMEN, P. E.: Retained lens fragments after phacoemulsification manifesting as market intraocular inflammation with hypopyon, 610

J

JAFFE, G. J., BURTON, T. C., KUHN, E., PRESCOTT, A., and HARTZ, A.: Progression of nonproliferative diabetic retinopathy and visual outcome after extracapsular cataract extraction and intraocular lens implantation, 448

JALKH, A.: See CHEN, S., 772

JAMPEL, H. D.: See HEHER, K. L., 771

JARVI, T. S.: See ZEITER, J. H., 758

JOHNS, D. R.: See THRELKELD, A. B., 322

JOHNS, K.: Essentials of Ophthalmology, by Bartley, G. B., and Liesegang, T. J. (book review), 112

JOHNSON, B. L., and HOLZMAN, A. E.: Ultrastructure of human immunodeficiency virus in corneal epithelial scraping (letter), 633

JOHNSON, B. L.: See DONAHUE, S. P., 639

JONAS, J. B.: See MEDENBLIK-FRYSCH, S., 230

JONES, F. R.: See RICHARDS, B. W., 777

JONES, I. S.: Bruce, Gordon M. 1901–1992 (obituary), 245

JONES, K.: See RODRIGUES, M., 161

JUZYCH, M. S.: See ZEITER, J. H., 758

K

KACZMAREK, R. G.: See SHARKNESS, C. M., 667

KAO, C.-S.: See CHEN, M.-S., 723

KARESH, J. W.: See HEMADY, R., 584

KASLOW, R. A.: See GLASNER, P. D., 136

KATLAMA, C.: See COCHEREAU-MASSIN I., 130

KATLAMA, C.: See REUX, I., 375

KATTLEMAN, B. S.: See ALBERT, D. L., 222

KATZ, B.: The Basics of Neuro-ophthalmology, by Farris, B. K. (ed.) (book review), 243

KATZ, H. R.: See SNYDER, M. E., 336

KATZEN, B. W.: See HEMADY, R., 584

KAUFMAN, H. E.: See CLINCH, T. E., 437

KAUFMAN, H. E.: See LINDSTROM, R. L., 345

KAUFMANN, J. G., DRIEBE, W., and MARGO, C. E.: *Streptococcus viridans*-induced crystalline keratopathy and fungal keratitis (letter), 97

KEECH, R. V.: See BAUTISTA, D. V., 635

KELLY, D. M.: See NUTAITIS, M. J., 297

KELLY, D. M.: See STEWART, W. C., 302

KETCHAM, J. M.: See HOLLAND, E. J., 182

KEUNEN, J. E. E.: See LIEM, A. T. A., 149

KHAW, P. T.: See SMITH, M. F., 737

KIM, D. D., MIELER, W. F., and WOLF, M. D.: Posterior segment changes in membranoproliferative glomerulonephritis, 593

KIM, E. K., GEROSKI, D. H., HOLLEY, G. P., URKEN, S. I., and EDELHAUSER, H. F.: Corneal endothelial cytoskeletal changes in F-actin with aging, diabetes, and after cytochalasin exposure, 329

KLAUSS, V.: See GEIER, S. A., 514

KODSI, S. R., and YOUNGE, B. R.: Acquired oculomotor, trochlear, and abducent cranial nerve palsies in pediatric patients, 568

KOONER, K. S., and GOODE, S. M.: Removable ligature during Molteno implant procedure (letter), 102

KOWAL, V. O., ADAMIS, A. P., and ALBERT, D. M.: Conjunctival concretions (letter), 640

KRAUS, E.: See RUMELT, S., 507

KRETZER, F. L.: See MINTZ-HITTNER, H. A., 700

KRINSKY, A. H.: See HUNTER, L. R., 373

KRONAWITTER, U.: See GEIER, S. A., 514

KRUPIN, T.: See HOLMWOOD, P. C., 19, 778

KRUSZON-MORAN, D.: See GLASNER, P. D., 136

KUHN, E.: See JAFFE, G. J., 448

KUNCL, R. W.: See THRELKELD, A. B., 322

KURTZBERG, J.: See NELSON, S. C., 23, 647, 648

KUSHNER, B. J.: Torsional diplopia after transantral orbital decompression and extraocular muscle surgery associated with Graves' orbitopathy (correspondence), 239

L

LAIBSON, P. R.: See RUBINFELD, R. S., 420

LAING, R. A.: See LINDSTROM, R. L., 345

LAKHANPAL, V., HUSAIN, D., and SCHOCKET, S. S.: Posterior capsulotomy as a complication of indirect laser photocoagulation, 600

LAM, B. L., NERAD, J. A., and THOMPSON, H. S.: Paroxysmal eyelid retractions (letter), 105

LAM, B. L.: See SIATKOWSKI, R. M., 625

LAM, S., and TESSLER, H. H.: Running nylon suture dissolution after penetrating keratoplasty (correspondence), 240

LAMBERT, H. M., CAPONE, A., JR., AABERG, T. M., STERNBERG, P., JR., MANDELL, B. A., and LOPEZ, P. F.: Reply to SABATES, F. N., and FLETCHER, D. C.: Surgical excision of subfoveal neovascular membranes in age-related macular degeneration (correspondence), 242

LAMBERT, H. M.: See GROSSNIKLAUS, H. E., 464

LAMBERT, H. M.: See LOPEZ, P. F., 101, 257

LAMBERT, H. M.: See MARTINEZ, J. A., 615

LAMBERT, H. M.: See STERNBERG, P., JR., 238

LAMBERT, S. R.: See GRIMMETT, M. R., 72

LANDERS, M. B., III: See COHEN, S. M., 697

LANE, S. S.: See HOLLAND, E. J., 182

LASS, J.: See LESHER, M. P., 231

LASS, J. H.: See LINDSTROM, R. L., 345

LAUTIER-FRAU, M.: See COCHEREAU-MASSIN I., 130

LAYCOCK, K. A.: See PEPOSE, J. S., 45

LAYCOCK, K. A.: See TALLEY, A. R., 685

LEE, B. L., MATOBA, A. Y., OSATA, M. S., and ROBINSON, N. M.: The solubility of antibiotic and corticosteroid combinations, 212

LEE, K. J.: See PEYMAN, G. A., 103, 648

LEE, M.: See CAMPOS, M., 429

LEE, P.: See MCDONNELL, P. J., 531

LEE, P. P.: See PRENDIVILLE, P., 397

LEHAR, M.: See THRELKELD, A. B., 322

LEHOANG, P.: See COCHEREAU-MASSIN I., 130

LEHOANG, P.: See REUX, I., 375

LEIBU, R.: See PORGES, Y., 30

LENZE, E. J.: See PEPOSE, J. S., 45

LEONE, C. R., JR.: Periosteal flap for lower eyelid reconstruction (letter), 513

LEPORT, C.: See COCHEREAU-MASSIN I., 130

LESHER, M. P., LOHMAN, L. E., YEAKLEY, W., and LASS, J.: Recurrence of herpetic stromal keratitis after a conjunctival flap surgical procedure (letter), 231

LESSELL, S.: See LIU, G. T., 193

LEVI, L., and FELDMAN, R. M.: Use of the potential acuity meter in suspected functional visual loss (letter), 502

LEWIS, H.: See MICHELS, M., 287

LIANG, K.: See CLINCH, T. E., 437

LIEBERMAN, M. F.: See STAMPER, R. L., 544

LIEBMANN, J.: See WESELEY, P., 539

LIEM, A. T. A., KEUNEN, J. E. E., and VAN NORREN, D.: Foveal densitometry in adult-onset diffuse drusen, 149

LIGGETT, P. E.: See ALFARO, D. V., 81

LIM, J. I.: See HEHER, K. L., 771

LINCOFF, H.: See DOLPHIN, K., 775

LINDSTROM, R. L., KAUFMAN, H. E., SKELNIK, D. L., LAING, R. A., LASS, J. H., MUSCH, D. C., TROUSDALE, M. D., REINHART, W. J., BURRIS, T. E., SUGAR, A., DAVIS, R. M., HIROKAWA, K., SMITH, T., and GORDON, J. F.: Optisol corneal storage medium, 345

LISCH, C.: See LISCH, W., 35

LISCH, W., STEUHL, K.-P., LISCH, C., WEIDLE, E. G., EMMIG, C.-T., COHEN, K. L., and PERRY, H. D.: A new, band-shaped and whorled microcystic dystrophy of the corneal epithelium, 35

LIU, G. T., and LESSELL, S.: Spontaneous visual improvement in chiasmal gliomas, 193

LOEFFELHOLZ, M.: See TALLEY, A. R., 685

LOHMAN, L. E.: See LESHER, M. P., 231

LOPEZ, P. F., AABERG, T. M., LAMBERT, H. M., STERNBERG, P., JR., and CAPONE, A., JR.: Choroidal neovascularization occurring within a demarcation line (letter), 101

LOPEZ, P. F., GROSSNIKLAUS, H. E., AABERG, T. M., STERNBERG, P., JR., CAPONE A., JR., and LAMBERT, H. M.: Pathogenetic mechanisms in anterior proliferative vitreoretinopathy, 257

LOPEZ, P. F.: See GROSSNIKLAUS, H. E., 464

LOPEZ, P. F.: See LAMBERT, H. M., 242

LOPEZ, P. F.: See MARTINEZ, J. A., 615

LOPEZ, P. F.: See STERNBERG, P., JR., 238

LOWRY, J. C.: See BARTLEY, G. B., 380

LUBNIEWSKI, A. J.: See HOLLAND, E. J., 182

LUEDER, G. T.: Successful therapy for trilateral retinoblastoma (correspondence), 646

LUSKY, M.: See BOSEM, M. E., 280

LYONS, L. A.: See MINTZ-HITTNER, H. A., 700

M

MACSAI, M. S.: Refractive Keratotomy for Myopia and Astigmatism, by Waring, G. O., III (ed.) (book review), 110

MACSAI, M. S.: Total detachment of Descemet's membrane after small-incision cataract extraction (letter), 365

MADION, M. P.: See ZEITER, J. H., 780

MAHANTI, R. L.: See HOLLAND, E. J., 680

MAIMONE, D.: See ABU EL ASRAR, A. M., 731

MANDELL, B. A.: See LAMBERT, H. M., 242

MANDELL, B. A.: See MARTINEZ, J. A., 615

MANNIS, M. J.: The History of Ophthalmology, vol. 10. The First and Second Half of the Nineteenth Century (Parts 9 to 17), by Hirschberg, J. (book review), 243

MANNIS, M. J.: Ocular Problems in Diabetes Mellitus, by Feman, S. S. (ed.) (book review), 783

MANSOUR, A. M., and RAZZUK, A. M.: Ocular injuries caused by misuse of an immersion heater (letter), 100

MARCEL, P.: See COCHEREAU-MASSIN I., 130

MARCUS, D. M., MAWN, L. A., EGAN, K. M., and ALBERT, D. M.: Nucleolar organizer regions in iris nevi and melanomas, 202

MARGO, C. E.: See KAUFMANN, J. G., 97

MARINES, H. M.: See DE LA PAZ, M. A., 208

MARTIN, D. F., and McCUEN, B. W., II: Efficacy of fluid-air exchange for postvitrectomy diabetic vitreous hemorrhage, 457

MARTINEZ, J. A., LOPEZ, P. F., STERNBERG, P., JR., AABERG, T. M., LAMBERT, H. M., CAPONE, A., JR., MANDELL, B. A., and NEWMAN, N. J.: Vogt-Koyanagi-Harada syndrome in patients with Cherokee indian ancestry, 615

MARTINEZ, J. A.: See GROSSNIKLAUS, H. E., 464

MARTINS, M. C.: See GLASNER, P. D., 136

MASKIN, S. L., and ALFONSO, E.: Fungal keratitis after radial keratotomy (letter), 369

MASUDA, K.: See NISHI, M., 603

MATHERS, W. D., and BILLBOROUGH, M.: Meibomian gland function and giant papillary conjunctivitis, 188

MATOBA, A. Y.: See LEE, B. L., 212

MAUMENEE, I. H.: See TRABOULSI, E. I., 579

MAURILLO, J. A., JR., WASSERMAN, B., ALLEE, S., and ROBINSON, L.: Reply to SHORR, N., and ENZER, Y. R.: Molded acrylic mouthguard to control bleeding at the hard palate graft site after eyelid reconstruction (correspondence), 780

MAWN, L. A.: See MARCUS, D. M., 202

McCARTNEY, D.: See SHAMI, M., 769

McCARTY, G. R.: See SILVERSTONE, D. E., 378

McCUEN, B. W., II: See MARTIN, D. F., 457

McDONALD, M. B., and BURGESS, S. K.: Contralateral occipital depression related to obstetric forceps injury to the eye, 318

McDONNELL, P. J., NOBE, J., GAUDERMAN, W. J., LEE, P., AIELLO, A., and TROUSDALE, M.: Community care of corneal ulcers, 531

McDONNELL, P. J.: See CAMPOS, M., 51, 429

MCDONNELL, P. J.: See PRENDIVILLE, P., 397

McG Steele, A.B.: Manual of Systematic Corneal Surgery, (book review), 244

McHENRY, J. G.: See ZEITER, J. H., 780

McLELLAN, T. G.: See FRIBERG, T. R., 767

McMENEMY, M. G.: See STAMPER, R. L., 544

MEDENBLIK-FRYSCH, S., VON DEN DRIESCH, P., JONAS, J. B., and MEYTHALER, F. H.: Ocular complications in Sweet's syndrome (letter), 230

MEHTA, N. J.: See PEYMAN, G. A., 508

MEISLER, D. M.: See MEYERS, S. J., 621

MENEZO, J. L.: See DÍAZ-LLOPIS, M., 742

MEYERS, S. J., VARLEY, G. A., MEISLER, D. M., CAMISA, C., and WANDER, A. H.: Conjunctival involvement in paraneoplastic pemphigus, 621

MEYTHALER, F. H.: See MEDENBLIK-FRYSCH, S., 230

MICHELS, M., LEWIS, H., ABRAMS, G. W., HAN, D. P., MIELER, W. F., and NEITZ, J.: Macular phototoxicity caused by fiberoptic endoillumination during pars plana vitrectomy, 287

MIELER, W. F.: See KIM, D. D., 593

MIELER, W. F.: See MICHELS, M., 287

MILLER, B.: See BEIRAN, I., 504

MILLER, B.: See PORGES, Y., 30

MILLER, B. A., YOUNGER, D. A., and FRIENDLY, D. S.: Treatment of acquired intermittent horizontal jerk nystagmus with baclofen (letter), 366

MILLER, J. K.: See PEPOSE, J. S., 45

MILLER, N. R.: See THRELKELD, A. B., 322

MILLS, R. A. D.: See BROOKS, J. G., JR., 371

MINTZ-HITTNER, H. A., FERRELL, R. E., LYONS, L. A., and KRETZER, F. L.: Criteria to detect minimal expressivity within families with autosomal dominant aniridia, 700

MIYATA, N.: See MOCHIZUKI, M., 123

MIZENER, M. W.: See HOLLAND, E. J., 680

MOCHIZUKI, M., WATANABE, T., YAMAGUCHI, K., YOSHIMURA, K., NAKASHIMA, S., SHIRAO, M., ARAKI, S., TAKATSUKI, K., MORI, S., and MIYATA, N.: Uveitis associated with human T-cell lymphotropic virus Type I, 123

MOCHIZUKI, M.: See NISHI, M., 603

MONCINO, M.: See NELSON, S. C., 23, 647, 648

MOORE, R. M., JR.: See SHARKNESS, C. M., 667

MORI, S.: See MOCHIZUKI, M., 123

MORI, S.: See NISHI, M., 603

MORSE, L. S.: See COHEN, S. M., 697

MORSE, P. H.: See ABU EL ASRAR, A. M., 731

MOSHFEGHI, D. M., FINGER, P. T., COHEN, R. B., CHOE, W., and SMILARI, T.: Visual recovery after radiation therapy of orbital lymphoma (letter), 645

MURRAY, B.: See GRAHAM, S. L., 221

MURRAY, T. G.: See IRVINE, W. D., 610

MUSCH, D. C.: See LINDSTROM, R. L., 345

N

NAKASHIMA, S.: See MOCHIZUKI, M., 123

NARDIN, G. F.: See ZIMMERMAN, T. J., 1, 8

NASEMANN, J.: See GEIER, S. A., 514

NAVEA, A.: See DÍAZ-LLOPIS, M., 742

NEITZ, J.: See MICHELS, M., 287

NELSON, J. D., GORDON, J. F., and CHIRON KERATOCONJUNCTIVITIS SICCA STUDY GROUP: Topical fibronectin in the treatment of keratoconjunctivitis sicca, 441

NELSON, S. C., FRIEDMAN, H. S., OAKES, W. J., HALPERIN, E. C., TIEN, R., FULLER, G. N., HOCKENBERGER, B., SCROGGS, M. W., MONCINO, M., KURTZBERG, J., and BUCKLEY, E. G.: Reply to ABRAMSON, DAVID H.: Successful therapy for trilateral retinoblastoma (correspondence), 648

NELSON, S. C., FRIEDMAN, H. S., OAKES, W. J., HALPERIN, E. C., TIEN, R., FULLER, G. N., HOCKENBERGER, B., SCROGGS, M. W., MONCINO, M., KURTZBERG, J., and BUCKLEY, E. G.: Reply to LUEDER, GREGG T.: Successful therapy for trilateral retinoblastoma (correspondence), 647

NELSON, S. C., FRIEDMAN, H. S., OAKES, W. J., HALPERIN, E. C., TIEN, R., FULLER, G. N., HOCKENBERGER, B., SCROGGS, M. W., MONCINO, M., KURTZBERG, J., and BUCKLEY, E. G.: Successful therapy for trilateral retinoblastoma, 23

NERAD, J. A.: See LAM, B. L., 105

NEWELL, F. W.: The obligation of ophthalmic organizations to report their actions (editorial), 220

NEWMAN, N. J.: See MARTINEZ, J. A., 615

NEWMAN, S. A.: Clinical Decisions in Neuro-Ophthalmology, ed. 2, by Burde, R. M., Savino, P. J., and Trobe, J. D. (book review), 381

NIRANKARI, V.: See RODRIGUES, M., 161

NISHI, M., HANASHIRO, R., MORI, S., MASUDA, K., MOCHIZUKI, M., and HONDO, R.: Polymerase chain reaction for the detection of the Varicella-zoster genome in ocular samples from patients with acute retinal necrosis, 603

NOBE, J.: See MCDONNELL, P. J., 531

NOGUCHI, B. A.: See WRIGHT, K. W., 409

NOVACK, G. D.: The development of new drugs for ophthalmology, 357

NUSSENBLATT, R. B.: See GLASNER, P. D., 136

NUTAITIS, M. J., STEWART, W. C., KELLY, D. M., HUNT, H. H., and SEVERNS, M. L.: Pattern discrimination perimetry in patients with glaucoma and ocular hypertension, 297

O

OAKES, W. J.: See NELSON, S. C., 23, 647, 648

OFNER, S., and SAMPLES, J. R.: Low-tension glaucoma in identical twins (letter), 764

OFNER, S., SAMPLES, J. R., and VAN BUSKIRK, E. M.: Apraclonidine and argon laser trabeculoplasty (correspondence), 778

OLANDER, K. W.: See SILVERSTONE, D. E., 378

OLIVER, J. M.: See SPAIDE, R. F., 515

OPHTH, F. C.: See SALMON, J. F., 766

ORGEL, I. K.: See PLAGER, D. A., 145

OSATA, M. S.: See LEE, B. L., 212

OSTERHOLM, M. T.: See HOLLAND, E. J., 680

OSTLER, H. B.: See SHERMAN, M. D., 233

P

PALLIKARIS, I. G., TSILIMBARIS, M. K., PAPATZANAKI, M. E., GOLES, K. G., and SIGANOS, D. S.: Paraformaldehyde-induced keratitis after photorefractive keratectomy, 339

PAPATZANAKI, M. E.: See PALLIKARIS, I. G., 339

PARKER, W. T.: See CLORFEINE, G. S., 229

PARKS, M. M.: See GREGG, F. M., 314

PARMLEY, V. C.: See WATERHOUSE, W., 510

PATRINELY, J. R.: See DE LA PAZ, M. A., 208

PAVLIN, C. J., HARASIEWICZ, K., and FOSTER, F. S.: Reply to BEZZINA, A. M.: Ultrasound biomicroscopy of anterior segment structures in normal and glaucomatous eyes (correspondence), 517

PEASE, M. E.: See VARMA, R., 554

PEPOSE, J. S., LAYCOCK, K. A., MILLER, J. K., CHANSUE, E., LENZE, E. J., GANS, L. A., and SMITH, M. E.: Reactivation of latent herpes simplex virus by excimer laser photokeratectomy, 45

PEPOSE, J. S., and WILHELMUS, K. R.: Divergent approaches to the management of corneal ulcers (editorial), 630

PEPOSE, J. S.: See TALLEY, A. R., 685

PERALTA, J., ABELAIRAS, J., and FERNÁNDEZ-GUARDIOLA, J.: Anaphylactic shock and death after oral intake of acetazolamide (letter), 367

PERRY, H. D.: See LISCH, W., 35

PERUSSE, P.: Localized distichiasis after tarsorrhaphy (letter), 104

PEYMAN, G. A., and LEE, K. J.: Multifunction endolaser probe (letter), 103

PEYMAN, G. A., and LEE, K. J.: Reply to CHANG, STANLEY: Multifunction endolaser probe (correspondence), 648

PEYMAN, G. A., and MEHTA, N. J.: Subretinal diathermy probe (letter), 508

PHILLIPS, C. I.: Trabeculectomy without conjunctival incision (correspondence), 108

PILLAI, S, and DiPAOLO, F.: Bilateral panuveitis, sebopsoriasis, and secondary syphilis in a patient with acquired immunodeficiency syndrome (letter), 773

PLAGER, D. A., ORGEL, I. K., ELLIS, F. D., HARTZER, M., TRESE, M. T., and SHASTRY, B. S.: X-Linked recessive familial exudative vitreoretinopathy, 145

PLOTNIK, R. D.: Grayson's Diseases of the Cornea, ed. 3, by Arffa, R. C. (book review), 518

PORGES, Y., GERSHONI-BARUCH, R., LEIBU, R., GOLDSCHER, D., ZONIS, S., SHAPIRA, I., and MILLER, B.: Hereditary microphthalmia with colobomatous cyst, 30

PRENDIVILLE, P., MCDONNELL, P. J., and LEE, P. P.: Glove perforations in ophthalmic surgery, 397

PRESCOTT, A.: See JAFFE, G. J., 448

PRUM, B. E., SHIELDS, S. R., SIMMONS, R. B., ECHELMAN, D. A., and SHIELDS, M. B.: The influence of exposure duration in transscleral Nd:YAG laser cyclophotocoagulation, 560

PUTTERMAN, A. M.: Color Atlas of Ophthalmic Surgery. Oculoplastic Surgery, by Tse., D. T., (ed.) (book review), 782

Q

QUIGLEY, H. A.: See VARMA, R., 554

R

RAIZMAN, M. B.: See HEMADY, R., 55

RAJAGOPALAN, S.: See RODRIGUES, M., 161

RAO, N. A.: See WALKER, J., 374

RAZ, J.: See SHEFFER, R. N., 494

RAZZUK, A. M.: See MANSOUR, A. M., 100

REDER, A. T.: See ABU EL ASRAR, A. M., 731

REHANY, U.: See RUMELT, S., 507

REIM, M.: See WOLF, S., 638

REINHART, W. J.: See LINDSTROM, R. L., 345

REUX, I., FILLET, A.-M., AGUT, H., KATLAMA, C., HAUW, J.-J., and LEHOANG, P.: In situ detection of human herpesvirus 6 in retinitis associated with acquired immunodeficiency syndrome (letter), 375

RICHARDS, B. W., JONES, F. R., and YOUNGE, B. R.: Reply to RUSH, J. A.: Causes and prognosis in 4,278 cases of paralysis of the oculomotor, trochlear, and abducens cranial nerves (correspondence), 777

RICHTER, C. U.: See WEISS, H. S., 14

RITCH, R., CHAIWAT, T., and HARBIN, T. S., JR.: Asymmetric pigmentary glaucoma resulting from cataract formation, 484

RITCH, R.: See WESELEY, P., 539

ROBINET, M.: See COCHEREAU-MASSIN I., 130

ROBINSON, L.: See MAURILLO, J. A., JR., 780

ROBINSON, M. J.: See CLINCH, T. E., 437

ROBINSON, N. M.: See LEE, B. L., 212

RODRIGUES, M., NIRANKARI, V., RAJAGOPALAN, S., JONES, K., and FUNDERBURGH, J.: Clinical and histopathologic changes in the host cornea after epikeratoplasty for keratoconus, 161

ROMANOWSKI, A.: Prophylactic use of apraclonidine for intraocular pressure increase after Nd:YAG capsulotomies (correspondence), 377

ROOTMAN, J.: Atlas of Orbital Surgery, by Leone, C. R., Jr., Grove, A. S., Jr., Lloyd, W. C., III, and Wojno, T. H. (book review), 381

ROSENBERG, L. F.: See HOLMWOOD, P. C., 19, 778

ROSMONDO, V., and BORCHERT, M.: Position-dependent Parinaud's syndrome (letter), 107

ROZENBAUM, W.: See COCHEREAU-MASSIN I., 130

RUBINFELD, R. S., SILBERT, D. I., ARENTSEN, J. J., and LAIBSON, P. R.: Ocular hydrofluoric acid burns, 420

RUBSAMEN, P. E.: See CALLANAN, D., 637

RUBSAMEN, P. E.: See IRVINE, W. D., 610

RUDERMAN, J. M.: See HOLMWOOD, P. C., 19, 778

RUMELT, S., KRAUS, E., and REHANY, U.: Retinal neovascularization and cystoid macular edema in punctate albescens retinopathy (letter), 507

RUNGE, P. E.: See FLEMING, T. N., 589

RUNYAN, T.: See ALFARO, D. V., 81

RUSH, J. A.: Causes and prognosis in 4,278 cases of paralysis of the oculomotor, trochlear, and abducens cranial nerves (correspondence), 777

RUSH, J. A.: Nonbacterial thrombotic endocarditis and cortical blindness (letter), 643

RYAN, S. J.: See ALFARO, D. V., 81

S

SABATES, F. N., and FLETCHER, D. C.: Surgical excision of subfoveal neovascular membranes in age-related macular degeneration (correspondence), 241

SAGGAU, D. D.: See GARRITY, J. A., 240

SALMON, J. F., and OPHTH, F. C.: The association of iridoschisis and angle-recession glaucoma (letter), 766

SAMPLES, J. R.: See OFNER, S., 764, 778

SANCHEZ, S.: See DÍAZ-LLOPIS, M., 742

SAXE, S. J., GROSSNIKLAUS, H. E., and SOMEREN, A. O.: Malignant myoepithelioma after radiation for retinoblastoma (letter), 512

SCHANZLIN, D. J.: See ASSIL, K. K., 63

SCHATZ, N. J.: See SIATKOWSKI, R. M., 625

SCHOCKET, S. S.: See LAKHANPAL, V., 600

SCHRADER, R. R.: Computerized Perimetry. A Simplified Guide, ed. 2, by Lieberman, M. F., and Drake, M. V. (book review), 785

SCHULTE, K.: See WOLF, S., 638

SCROGGS, M. W.: See NELSON, S. C., 23, 647, 648

SEVERNS, M. L.: See NUTAITIS, M. J., 297

SHAHINIAN, L., JR., EGBERT, P. R., and WILLIAMS, A. S.: Histologic study of healing after ab interno laser sclerostomy, 216

SHAMI, M., MCCARTNEY, D., BENEDICT, W., and BARNES, C.: Spontaneous retinal reattachment in a patient with persistent hyperplastic primary vitreous and an optic nerve coloboma (letter), 769

SHAMI, M.: See BENEDICT, W. L., 765

SHAPIRA, I.: See PORGES, Y., 30

SHARIR, M.: See ZIMMERMAN, T. J., 1, 8

SHARKNESS, C. M., HAMBURGER, S., KACZMAREK, R. G., HAMILTON, P. M., BRIGHT, R. A., and MOORE, R. M., JR.: Racial differences in the prevalence of intraocular lens implants in the United States, 667

SHARMA, O. P.: See WALKER, J., 374

SHARP, G. B.: See BRODSKY, M. C., 509

SHASTRY, B. S.: See PLAGER, D. A., 145

SHEFFER, R. N., ZLOTOGORA, J., ELPELEG, O. N., RAZ, J., and BEN-EZRA, D.: Behr's syndrome and 3-methylglutaconic aciduria, 494

SHERMAN, M. D., OSTLER, H. B., BISWELL, R., and CEVALLOS, V.: *Enterococcus faecalis* infection in a corneal graft (letter), 233

SHERWOOD, M. B.: See SMITH, M. F., 737

SHIELDS C. L.: See SHIELDS, J. A., 227

SHIELDS, J. A., SHIELDS C. L., EAGLE, R. C., DE POTTER, P., and DOUGLAS, C. H.: Calcified intraocular abscess simulating retinoblastoma (letter), 227

SHIELDS, M. B.: See PRUM, B. E., 560

SHIELDS, S. R.: See PRUM, B. E., 560

SHIN, D. H.: See ZEITER, J. H., 758

SHINGLETON, B. J.: See WEISS, H. S., 14

SHIRAO, M.: See MOCHIZUKI, M., 123

SHORR, N., and ENZER, Y. R.: Molded acrylic mouthguard to control bleeding at the hard palate graft site after eyelid reconstruction (correspondence), 779

SIATKOWSKI, R. M., LAM, B. L., SCHATZ, N. J., GLASER, J. S., BYRNE, S. F., and HUGHES, J. R.: Optic neuropathy in Hodgkin's disease, 625

SIGANOS, D. S.: See PALLIKARIS, I. G., 339

SILBERT, D. I.: See RUBINFELD, R. S., 420

SILVEIRA, C.: See GLASNER, P. D., 136

SILVEIRA, S.: See GLASNER, P. D., 136

SILVERSTONE, D. E., BRINT, S. F., OLANDER, K. W., TAYLOR, R. B., MCCARTY, G. R., DEFALLER, J. M., and BURK, L. L.: Reply to ROMANOWSKI, A.: Prophylactic use of apraclonidine for intraocular pressure increase after Nd:YAG capsulotomies (correspondence), 378

SIMCOE, W.: Management and Care of the Cataract Patient, by Weinstock, F. J. (ed.) (book review), 785

SIMMONS, R. B.: See PRUM, B. E., 560

SIMON, J. W.: See CHEN, T. C., 575

SIVALINGHAM, A.: See WALLACE, R. T., 158

SKELNIK, D. L.: See LINDSTROM, R. L., 345

SKUTA, G. L.: Automated Static Perimetry, by Anderson, D. R. (book review), 110

SMILARI, T.: See MOSHFEGHI, D. M., 645

SMITH, D. R.: See EUSTIS, H. S., 307

SMITH, M. E.: Intraocular Tumors. A Text and Atlas, by Shields, J. A., and Shields, C. L. (book review), 112

SMITH, M. E.: See PEPOSE, J. S., 45

SMITH, M. F., SHERWOOD, M. B., DOYLE, J. W., and KHAW, P. T.: Results of intraoperative 5-fluorouracil supplementation on trabeculectomy for open-angle glaucoma, 737

SMITH, T.: See LINDSTROM, R. L., 345

SNYDER, M. E., and KATZ, H. R.: Ciprofloxacin-resistant bacterial keratitis, 336

SOMEREN, A. O.: See SAXE, S. J., 512

SOSSI, N. P.: See FRUEH, B. E., 240

SPAETH, G. L.: The obligation of Ophthalmic organizations to report their actions (correspondence), 649

SPAIDE, R. F., VITALE, A. T., TOTH, I. R., and OLIVER, J. M.: Reply to GEIER, S. A., NASEMANN, J., KLAUSS, V., KRONAWITTER, U., and GOEBEL, F. D.: Frosted branch angiitis associated with cytomegalovirus retinitis (correspondence), 515

SPECTOR, R. T.: Neuro-Ophthalmology. A Practical Text, by Newman, N. M. (book review), 519

SPOOR, T. C.: See ZEITER, J. H., 758

STAMPER, R. L., MCMENEMY, M. G., and LIEBERMAN, M. F.: Hypotonous maculopathy after trabeculectomy with subconjunctival 5-fluorouracil, 544

STERNBERG, P., JR., LAMBERT, H. M., CAPONE, A., LOPEZ, P. F., and AABERG, T. M.: Reply to HINDLE, N. W.: Controversies in the management of retinopathy of prematurity (correspondence), 238

STERNBERG, P., JR.: See GROSSNIKLAUS, H. E., 464

STERNBERG, P., JR.: See LAMBERT, H. M., 242

STERNBERG, P., JR.: See LOPEZ, P. F., 101, 257
STERNBERG, P., JR.: See MARTINEZ, J. A., 615
STEUHL, K.-P.: See LISCH, W., 35
STEWART, W. C., KELLY, D. M., and HUNT, H. H.: Long-term and short-term fluctuation in pattern discrimination perimetry, 302
STEWART, W. C.: See NUTAITIS, M. J., 297
STROH, E. M.: See CHEN, S., 772
STULTING, R. D.: See BRUNETTE, I., 370
SUGA, J.: See YAZAWA, K., 416
SUGAR, A.: See LINDSTROM, R. L., 345
SUMITOMO, M.: See YAZAWA, K., 416

T

TAI, T.-Y.: See CHEN, M.-S., 723
TAKATSUKI, K.: See MOCHIZUKI, M., 123
TALLEY, A. R., GARCIA-FERRER, F., LAYCOCK, K. A., LOEFFELHOLZ, M., and PEPOSE, J. S.: The use of polymerase chain reaction for the detection of chlamydial keratoconjunctivitis, 685
TALLMAN, B. A.: See HOLMWOOD, P. C., 19, 778
TAYLOR, R. B.: See SILVERSTONE, D. E., 378
TESSLER, H. H.: See LAM, S., 240
THOMPSON, H. S.: The Fragile Species, by Thomas, L. (book review), 652
THOMPSON, H. S.: See LAM, B. L., 105
THRELKELD, A. B., MILLER, N. R., GOLNIK, K. C., GRIFFIN, J. W., KUNCL, R. W., JOHNS, D. R., LEHAR, M., and HURKO, O.: Ophthalmic involvement in myo-neuro-gastrointestinal encephalopathy syndrome, 322
TIEN, R.: See NELSON, S. C., 23, 647, 648
TOTH, I. R.: See SPAIDE, R. F., 515
TRABOULSI, E. I., DE BECKER, I., and MAUMENEE, I. H.: Ocular findings in Cockayne syndrome, 579
TRAN, V. T.: See ALFARO, D. V., 81
TRESE, M. T.: See PLAGER, D. A., 145
TRIMBLE, S. N.: See EVANS, L. S., 224
TROUSDALE, M.: See McDONNELL, P. J., 531
TROUSDALE, M. D.: See LINDSTROM, R. L., 345
TSILIMBARIS, M. K.: See PALLIKARIS, I. G., 339

U

UEMURA, Y.: See YAZAWA, K., 416
URKEN, S. I.: See KIM, E. K., 329

V

VAN BUSKIRK, E. M.: Reply to PHILLIPS, C. I.: Trabeculectomy without conjunctival incision (correspondence), 109
VAN BUSKIRK, E. M.: See OFNER, S., 778
VAN DE GRAAFF, W. B.: See EVANS, L. S., 224
VAN DEN BERG, T. J. T. P.: See VERAART, H. G. N., 424
VAN NORREN, D.: See LIEM, A. T. A., 149
VARLEY, G. A.: See MEYERS, S. J., 621
VARMA, R., QUIGLEY, H. A., and PEASE, M. E.: Changes in optic disk characteristics and the number of nerve fibers in experimental glaucoma, 554
VERAART, H. G. N., VAN DEN BERG, T. J. T. P., IJSPEERT, J. K., and CARDOZO, O. L.: Stray light in radial keratotomy and the influence of pupil size and straylight angle, 424
VITALE, A. T.: See SPAIDE, R. F., 515
VON DEN DRIESCH, P.: See MEDENBLIK-FRYSCH, S., 230
VON NOORDEN, G. K.: Recession of both horizontal recti muscles in Duane's retraction syndrome with elevation and depression of the adducted eye, 311
VRABEC, M. P., DURRIE, D. S., and CHASE, D. S.: Recurrence of herpes simplex after excimer laser keratectomy (letter), 96
VRABEC, M. P.: See DEMATTEO, M. P., 99

W

WAGLE, W. A.: See CHEN, T. C., 575
WAKITA, S.: See YAZAWA, K., 416
WALD, K.: See CHEN, S., 772
WALKER, J., SHARMA, O. P., and RAO, N. A.: Brucellosis and uveitis (letter), 374
WALLACE, R. T., BROWN, G. C., BENSON, W., and SIVALINGHAM, A.: Sudden retinal manifestations of intranasal cocaine and methamphetamine abuse, 158
WALSH, J. B.: See WESELEY, P., 539
WANDER, A. H.: See MEYERS, S. J., 621
WASSERMAN, B.: See MAURILLO, J. A., JR., 780
WATANABE, T.: See MOCHIZUKI, M., 123
WATERHOUSE, W., ENZENAUER, R. W., and PARMLEY, V. C.: Inflammatory oribital tumor as an ocular sign of a battered child (letter), 510
WAUBKE, T.: See HÖPPING, W., 246
WEIDLE, E. G.: See LISCH, W., 35
WEINBERG, M. H.: See CHEN, T. C., 575
WEINREB, R. N.: See BOSEM, M. E., 280
WEISS, H. S., SHINGLETON, B. J., GOODE, S. M., BELLOWS, A. R., and RICHTER, C. U.: Argon laser gonioplasty in the treatment of angle-closure glaucoma, 14
WESELEY, P., LIEBMANN, J., WALSH, J. B., and RITCH, R.: Lattice degeneration of the retina and the pigment dispersion syndrome, 539
WESSING, A.: See HÖPPING, W., 246
WILHELMUS, K. R.: See PEPOSE, J. S., 630
WILLIAMS, A. S.: See SHAHINIAN, L., JR., 216
WILLIAMS, J. W.: See GOSSMAN, M. D., 379
WIZNIA, R. A.: Development of a retinal artery macroaneurysm at the site of a previously detected retinal artery embolus (letter), 642
WOLF, M. D.: See KIM, D. D., 593

WOLF, S., AREND, O., SCHULTE, K., and REIM, M.: Severe anaphylactic reaction after indocyanine green fluorescence angiography (letter), 638
WRIGHT, K. W., CHRISTENSEN, L. E., and NOGUCHI, B. A.: Results of late surgery for presumed congenital cataracts, 409
WRIGHT, M. M.: Glaucoma Surgery, by Thomas, J. V. (ed.) (book review), 111
WU, T.-J.: See CHEN, M.-S., 723

Y

YAMAGUCHI, K.: See MOCHIZUKI, M., 123
YAP, E.-Y., and BUETTNER, H.: Traumatic rupture of a persistent hyaloid artery (letter), 225
YAZAWA, K., SUGA, J., WAKITA, S., SUMITOMO, M., and UEMURA, Y.: The Tokyo metropolitan home vision screening program for amblyopia in 3-year-old children, 416
YEAKLEY, W.: See LESHER, M. P., 231
YOSHIMURA, K.: See MOCHIZUKI, M., 123
YOUNGE, B. R.: See KODSI, S. R., 568
YOUNGE, B. R.: See RICHARDS, B. W., 777
YOUNGER, D. A.: See MILLER, B. A., 366
YUNG, R.: See GOSSMAN, M. D., 379

Z

ZARNEGAR, S. R.: See ASSIL, K. K., 63
ZAZOUN, L.: See COCHEREAU-MASSIN I., 130
ZEITER, J. H., CORDER, D. M., MADION, M. P., and McHENRY, J. G.: Sudden retinal manifestations of intranasal cocaine and methamphetamine abuse (correspondence), 780
ZEITER, J. H., SHIN, D. H., JUZYCH, M. S., JARVI, T. S., SPOOR, T. C., and ZWAS, F.: Visual field defects in patients with normal-tension glaucoma and patients with high-tension glaucoma, 758
ZERDOUN, E.: See COCHEREAU-MASSIN I., 130
ZIMMERMAN, A.: See HEMADY, R., 584
ZIMMERMAN, T. J., SHARIR, M., NARDIN, G. F., and FUQUA, M.: Therapeutic index of epinephrine and dipivefrin with nasolacrimal occlusion, 8
ZIMMERMAN, T. J., SHARIR, M., NARDIN, G. F., and FUQUA, M.: Therapeutic index of pilocarpine, carbachol, and timolol with nasolacrimal occlusion, 1
ZLOTOGORA, J.: See SHEFFER, R. N., 494
ZONIS, S.: See PORGES, Y., 30
ZWAS, F.: See ZEITER, J. H., 758

ABSTRACT INDEX

A

Acquired immunodeficiency syndrome
AIDS and the conundrum of job, 527
Role of HIV and CMV in the pathogenesis of retinitis ana retinal vasculopathy in AIDS patients, 657
Selective loss of optic nerve β-tubulin in vincristine-induced blindness, 791

Acute retinal necrosis
Systemic antiviral drugs used in ophthalmology, 657

Acyclovir
Acyclovir. A decade later, 793

Aging
Alzheimer's disease. The amyloid cascade hypothesis, 249
Corneal arcus and cardiovascular risk factors in Asians in Singapore, 655
Mitochondrial genetics. A paradigm for aging and degenerative diseases?, 249

Allergy
Medical therapy for ocular allergy, 388

Alzheimer's disease
Alzheimer's disease. The amyloid cascade hypothesis, 249

Amyloid plaque
Alzheimer's disease. The amyloid cascade hypothesis, 249

Analgesia
Intraoperative patient-controlled analgesia. An alternative to physician administration during outpatient monitored anesthesia care, 660

Anesthesia
Biological roles of nitric oxide, 389
Current practice of cataract extraction and anaesthesia, 391
Intraoperative patient-controlled analgesia. An alternative to physician administration during outpatient monitored anesthesia care, 660

Angiography
Digital indocyanine green videoangiography and choroidal neovascularization, 789

Anhidrosis
Tonic pupil, areflexia, and segmental anhidrosis. Two additional cases of Ross syndrome and review of the literature, 391

Antigen
Superantigens in human disease, 250

Apraclonidine
Apraclonidine hydrochloride as an adjunct to timolol maleate therapy, 788

Arachnodactyly
Genetic linkage of the Marfan syndrome, ectopia lentis, and congenital contractural arachnodactyly to the fibrillin genes on chromosomes 15 and 5, 114

Artery
Presenting features and outcomes in patients undergoing temporal artery biopsy. A review of 98 patients, 791

Aspirin
Surgical bleeding associated with aspirin and nonsteroidal anti-inflammatory agents, 120

B

Benedikt's syndrome
Midbrain syndromes of Benedikt, Claude, and Nothnagel. Setting the record straight, 791

Beta-blocker
Reduced ocular hypotensive effect of topical β-blockers in glaucoma patients receiving oral β-blockers, 788

Biopsy
Presenting features and outcomes in patients undergoing temporal artery biopsy. A review of 98 patients, 791

Bleb
Same-site revision of failed filtering blebs, 116

Blepharospasm
A new variant of blepharospasm, 524

Blind spot
Blind spots, 388

Botulinum toxin
Botulinum toxin treatment of supranuclear ocular motility disorders, 523

C

Carcinoma
Basal cell carcinoma in young adults, 660

Carotid
Results of a randomized controlled trial of carotid endarterectomy for asymptomatic carotid stenosis, 385

Cataract
Current practice of cataract extraction and anaesthesia, 391
Endophthalmitis following extracapsular cataract surgery. A review of 32 cases, 521
Of sight and song, 527
Phantom limbs, 391
Premedication for outpatient cataract surgery. A comparative study of intramuscular alfentanil, midazolam and placebo, 660

A prospective study of cigarette smoking and risk of cataract in men, 655
A prospective study of cigarette smoking and risk of cataract surgery in women, 655
Use of intraocular lenses in cataract surgery in developing countries, 115

Central retinal vein
Role of diabetes mellitus on the natural history of central retinal vein occlusion, 251

Children
Cortical blindness in children. Utility of flash VEPs, 386
Head injury in very young children. Mechanisms, injury types, and ophthalmologic findings in 100 hospitalized patients younger than 2 years of age, 789
Oral administration of tranexamic acid in the management of traumatic hyphema in children, 656
Preschool vision screening in pediatric practice. A study from the Pediatric Research in Office Settings (PROS) Network, 391
Reading skills and auditory processing ability in children with chronic otitis media in early childhood, 525
Should children drink before discharge from day surgery?, 251

***Chlamydia* sp.**
A controlled trial of a single dose of azithromycin for the treatment of chlamydial urethritis and cervicitis, 793

Choroid
Digital indocyanine green videoangiography and choroidal neovascularization, 789

Cicatricial pemphigoid
Improved detection of disease progression in ocular cicatricial pemphigoid, 788

Claude's syndrome
Midbrain syndromes of Benedikt, Claude, and Nothnagel. Setting the record straight, 791

Color vision
Detection of colour vision abnormalities in uncomplicated type 1 diabetic patients with angiographically normal retinas, 657

Conjunctiva
Conjunctival impression cytology with transfer as a field-applicable indicator of vitamin A status for mass screening, 654
Impression cytology of conjunctival melanosis and melanoma, 247
Multifocal amelanotic conjunctival melanoma and acquired melanosis sine pigmento, 247

Conjunctivitis
Medical therapy for ocular allergy, 388

Cornea
Corneal arcus and cardiovascular risk factors in Asians in Singapore, 655
Corneal storage medium preservation with defensins, 787
Corneal topographic changes over time after radial keratotomy, 787
Evaluation of corneal topography, 787
Improved detection of disease progression in ocular cicatricial pemphigoid, 788
Wound healing of the ocular surface, 252

Cortex
Phantom limbs, 391

Cromolyn sodium
Alternative solution for Opticrom, 654

Cyclosporine
Risk factors for cyclosporine-induced nephropathy in patients with autoimmune diseases, 390

Cytomegalovirus
Restoration of viral immunity in immunodeficient humans by the adoptive transfer of T cell clones, 526
Role of HIV and CMV in the pathogenesis of retinitis ana retinal vasculopathy in AIDS patients, 657
Systemic antiviral drugs used in ophthalmology, 657

D

Diabetes mellitus
Detection of colour vision abnormalities in uncomplicated type 1 diabetic patients with angiographically normal retinas, 657
Risk factors for cyclosporine-induced nephropathy in patients with autoimmune diseases, 390
Role of diabetes mellitus on the natural history of central retinal vein occlusion, 251

Disk
Platelet aggregation, disc haemorrhage and progressive loss of visual fields in glaucoma. A seven year follow-up on glaucoma, 248

Donor
Corneal storage medium preservation with defensins, 787

Droperidol
A double-blinded comparison of metoclopramide and droperidol for prevention of emesis following strabismus surgery, 119

E

Ectopia lentis
Genetic linkage of the Marfan syndrome, ectopia lentis, and congenital contractural arachnodactyly to the fibrillin genes on chromosomes 15 and 5, 114

Electrocautery
The mutagenicity of electrocautery smoke, 247

Endarterectomy
Results of a randomized controlled trial of carotid endarterectomy for asymptomatic carotid stenosis, 385

Endophthalmitis
Endophthalmitis following extracapsular cataract surgery. A review of 32 cases, 521

Epidermal growth factor
Wound healing of the ocular surface, 252
Evolution
The evolution of eyes, 119
Eyebrow
The brow slide. A technique for the aesthetic treatment of eyebrow tumors, 120
Eyelid
Malignant melonoma of the eyelid. A report of eight cases and a review of the literature, 525
Present status of eyelid phototherapy. Clinical efficacy and transmittance of ultraviolet and visible radiation through human eyelids, 250
Temporoparietal fascial flap for orbital and eyelid reconstruction, 386

F

Filtration
Same-site revision of failed filtering blebs, 116
Fundus
Fundus hemorrhages in infancy, 658

G

Genetics
Classification and staging of lymphoma by molecular genetics, 253
Genetic linkage of the Marfan syndrome, ectopia lentis, and congenital contractural arachnodactyly to the fibrillin genes on chromosomes 15 and 5, 114
Mitochondrial genetics. A paradigm for aging and degenerative diseases?, 249
Sinonasal primitive neuroectodermal tumor arising in a long-term survivor of heritable unilateral retinoblastoma, 658
The surgeon, genetics, and malignant melanoma, 116
Giant cell arteritis
Management of suspected giant cell arteritis, 790
Glaucoma
Apraclonidine hydrochloride as an adjunct to timolol maleate therapy, 788
Long-term post trabeculectomy intraocular pressures, 522
Of sight and song, 527
Platelet aggregation, disc haemorrhage and progressive loss of visual fields in glaucoma. A seven year follow-up on glaucoma, 248
Reduced ocular hypotensive effect of topical β-blockers in glaucoma patients receiving oral β-blockers, 788
Same-site revision of failed filtering blebs, 116
Static versus kinetic testing in the nasal peripheral field in patients with glaucoma, 115
Globe
Measurement of globe position in complex orbital fractures. I. A modification of Hertel's exophthalmometer, using the external auditory canal as a reference point, 387
Graves' ophthalmopathy
Antibodies to orbital tissues in thyroid-associated ophthalmopathy, 252
Graves' ophthalmopathy in relation to cigarette smoking and ethnic origin, 253
Immunosuppressive treatment of Graves' ophthalmopathy, 792
Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism, 524

H

Health care
Pharmaceutical promotions. A free lunch?, 794
Should you operate on your own mother?, 661
Health care delivery
Measuring and managing quality of surgery. Statistical vs incidental approaches, 526
Hematoma
Bleeding time. Is it a useful clinical tool?, 120
Hemianopsia
Postural disturbances due to homonymous hemianopic visual ataxia, 386
Hemiparesis
Midbrain syndromes of Benedikt, Claude, and Nothnagel. Setting the record straight, 791
Hemangioma
Interferon alfa-2a therapy for life-threatening hemangiomas of infancy, 389
Hemorrhage
Factors related to the incidence of secondary haemorrhage in 462 patients with traumatic hyphema, 656
Fundus hemorrhages in infancy, 658
Platelet aggregation, disc haemorrhage and progressive loss of visual fields in glaucoma. A seven year follow-up on glaucoma, 248
Terson's syndrome. A reversible cause of blindness following subarachnoid hemorrhage, 388
Hepatitis
Hepatitis B and hepatitis C in emergency department patients, 387
Herpes simplex
Acyclovir. A decade later, 793
In vivo gene transfer with retroviral vector-producer cells for treatment of experimental brain tumors, 390
Systemic antiviral drugs used in ophthalmology, 657
Herpes zoster
Systemic antiviral drugs used in ophthalmology, 657
History of ophthalmology
Benedit Duddell. Pioneer oculist of the 18th century, 527
Human immunodeficiency virus
Hepatitis B and hepatitis C in emergency department patients, 387

Role of HIV and CMV in the pathogenesis of retinitis ana retinal vasculopathy in AIDS patients, 657

Systemic antiviral drugs used in ophthalmology, 657

Vaccine protection of chimpanzees against challenge with HIV-1-infected peripheral blood mononuclear cells, 390

Hypertrophy
Congenital hypertrophy of retinal pigment epithelium in patients with colonic polyps associated with cancer family syndrome, 789

Hyphema
Factors related to the final visual outcome of 425 patients with traumatic hyphaema, 656

Factors related to the incidence of secondary haemorrhage in 462 patients with traumatic hyphema, 656

Oral administration of tranexamic acid in the management of traumatic hyphema in children, 656

I

Impression cytology
Conjunctival impression cytology with transfer as a field-applicable indicator of vitamin A status for mass screening, 654

Impression cytology of conjunctival melanosis and melanoma, 247

Indocyanine green
Digital indocyanine green videoangiography and choroidal neovascularization, 789

Infants
Fundus hemorrhages in infancy, 658

Head injury in very young children. Mechanisms, injury types, and ophthalmologic findings in 100 hospitalized patients younger than 2 years of age, 789

Interferon alfa-2a therapy for life-threatening hemangiomas of infancy, 389

Light and retinopathy of prematurity. Does retinal location offer a clue?, 385

Injury
Head injury in very young children. Mechanisms, injury types, and ophthalmologic findings in 100 hospitalized patients younger than 2 years of age, 789

Interferon
Disease stabilization by leukocyte alpha interferon and survival of patients with metastatic melanoma, 117

Intraocular lens
An analysis of intraocular lens exchange, 521

Use of intraocular lenses in cataract surgery in developing countries, 115

Intraocular pressure
Long-term post trabeculectomy intraocular pressures, 522

Same-site revision of failed filtering blebs, 116

Ischemia
Migraine aura without headache. Transient ischaemic attack or not?, 522

Predictors of postoperative myocardial ischemia in patients undergoing noncardiac surgery, 526

K

Kaposi's sarcoma
Selective loss of optic nerve β-tubulin in vincristine-induced blindness, 791

Kearns-Sayre syndrome
Endocrine dysfunction in Kearns-Sayre syndrome, 659

Keratoconjunctivitis
Medical therapy for ocular allergy, 388

Keratoconus
Prevalence of mitral valve prolapse in keratoconus patients, 654

L

Lacrimal apparatus
Fractures of the nasolacrimal fossa and canal. A CT study of appearance, associated injuries, and significance in 25 patients, 524

Reconstruction of the lacrimal excretory system, 792

Leukocyte
Disease stabilization by leukocyte alpha interferon and survival of patients with metastatic melanoma, 117

Low-vision aids
Psychophysics of reading. Clinical predictors of low-vision reading speed, 117

Lymphoma
Classification and staging of lymphoma by molecular genetics, 253

M

Magnetic resonance imaging
Fat-suppression MR imaging in neuroradiology. Techniques and clinical application, 118

Marfan syndrome
Genetic linkage of the Marfan syndrome, ectopia lentis, and congenital contractural arachnodactyly to the fibrillin genes on chromosomes 15 and 5, 114

Medical education
Who's first on first?, 528

Medical practice
Alteration of medical records submitted for medicolegal review, 251

The plastic surgeon knows best. A hazardous assumption, 254

Melanoma
Disease stabilization by leukocyte alpha interferon and survival of patients with metastatic melanoma, 117

Disseminated melanoma. Is there a new standard therapy?, 660

Impression cytology of conjunctival melanosis and melanoma, 247

Malignant melonoma of the eyelid. A report of eight cases and a review of the literature, 525

Multifocal amelanotic conjunctival melanoma and acquired melanosis sine pigmento, 247

'On' response defect in paraneoplastic night blindness with cutaneous malignant melanoma, 116

Regression of primary melanoma with metastases, 117

The surgeon, genetics, and malignant melanoma, 116

Treatment of metastatic malignant melanoma with dacarbazine plus tamoxifen, 659

Uveal melanoma. Therapeutic consequences of doubling times and irradiation results. A review, 385

Membrane
The patch clamp technique, 119

Meningioma
Meningiomas are not significantly associated with breast cancer, 658

Precision radiation therapy for optic nerve sheath meningiomas, 387

Metoclopramide
A double-blinded comparison of metoclopramide and droperidol for prevention of emesis following strabismus surgery, 119

Migraine
Migraine aura without headache. Transient ischaemic attack or not?, 522

Mitochondria
Mitochondrial genetics. A paradigm for aging and degenerative diseases?, 249

Motility
Botulinum toxin treatment of supranuclear ocular motility disorders, 523

Eye movements in myotonic dystrophy, 523

Muscle
Aetiology and management of the 'detached' rectus muscle, 253

Myopathy
Endocrine dysfunction in Kearns-Sayre syndrome, 659

Myotonic dystrophy
Eye movements in myotonic dystrophy, 523

N

Neuropathy
Risk of early-onset proliferative retinopathy in IDDM is closely related to cardiovascular autonomic neuropathy, 252

Night blindness
'On' response defect in paraneoplastic night blindness with cutaneous malignant melanoma, 116

Nothnagel's syndrome
Midbrain syndromes of Benedikt, Claude, and Nothnagel. Setting the record straight, 791

O

Oculomotor nerve
Evolution of oculomotor nerve palsies, 118

Midbrain syndromes of Benedikt, Claude, and Nothnagel. Setting the record straight, 791

Reconstruction of the third through sixth cranial nerves during cavernous sinus surgery, 523

Ophthalmopathy
Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism, 524

Optic atrophy
Of sight and song, 527

Optic nerve
Precision radiation therapy for optic nerve sheath meningiomas, 387

Selective loss of optic nerve β-tubulin in vincristine-induced blindness, 791

Orbit
Antibodies to orbital tissues in thyroid-associated ophthalmopathy, 252

Measurement of globe position in complex orbital fractures. I. A modification of Hertel's exophthalmometer, using the external auditory canal as a reference point, 387

Severe orbital infection as a complication of orbital fracture, 792

Temporoparietal fascial flap for orbital and eyelid reconstruction, 386

P

Palsy
Evolution of oculomotor nerve palsies, 118

Facial palsy and infection. The unfolding story, 114

Midbrain syndromes of Benedikt, Claude, and Nothnagel. Setting the record straight, 791

Perimetry
Factors influencing normal perimetric thresholds obtained using the Humphrey Field Analyzer, 115

Static versus kinetic testing in the nasal peripheral field in patients with glaucoma, 115

Platelet
Circadian variation in platelet function in healthy volunteers, 248

Pterygium
Pterygium treated with excision and postoperative beta irradiation, 521

Pupil
Computerized analysis of pupillograms in studies of alertness, 118

Pupillary escape, 522

Tonic pupil, areflexia, and segmental anhidrosis. Two additional cases of Ross syndrome and review of the literature, 391

R

Radial keratotomy
Corneal topographic changes over time after radial keratotomy, 787

Radiation
Precision radiation therapy for optic nerve sheath meningiomas, 387

Present status of eyelid phototherapy. Clinical efficacy and transmittance of ultraviolet and visible radiation through human eyelids, 250

Pterygium treated with excision and postoperative beta irradiation, 521

Uveal melanoma. Therapeutic consequences of doubling times and irradiation results. A review, 385

Reiter's syndrome
An acute remission of Reiter's syndrome in male patients treated with bromocriptine, 525

Retina
Detection of colour vision abnormalities in uncomplicated type 1 diabetic patients with angiographically normal retinas, 657

Light and retinopathy of prematurity. Does retinal location offer a clue?, 385

Retinal pigment epithelium
Congenital hypertrophy of retinal pigment epithelium in patients with colonic polyps associated with cancer family syndrome, 789

Retinoblastoma
Sinonasal primitive neuroectodermal tumor arising in a long-term survivor of heritable unilateral retinoblastoma, 658

Retinopathy
Risk of early-onset proliferative retinopathy in IDDM is closely related to cardiovascular autonomic neuropathy, 252

Retinopathy of prematurity
A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity, 248

Light and retinopathy of prematurity. Does retinal location offer a clue?, 385

Of sight and song, 527

Retinopathy of prematurity, 249

S

Sjögren's syndrome
Risk factors for cyclosporine-induced nephropathy in patients with autoimmune diseases, 390

***Staphylococcus* sp.**
Endophthalmitis following extracapsular cataract surgery. A review of 32 cases, 521

Strabismus
Aetiology and management of the 'detached' rectus muscle, 253

A double-blinded comparison of metoclopramide and droperidol for prevention of emesis following strabismus surgery, 119

Surgery
Should children drink before discharge from day surgery?, 251

T

T cell
Restoration of viral immunity in immunodeficient humans by the adoptive transfer of T cell clones, 526

Superantigens in human disease, 250

Terson's syndrome
Terson's syndrome. A reversible cause of blindness following subarachnoid hemorrhage, 388

Timolol
Apraclonidine hydrochloride as an adjunct to timolol maleate therapy, 788

Trabeculectomy
Long-term post trabeculectomy intraocular pressures, 522

Trigeminal nerve
Reconstruction of the third through sixth cranial nerves during cavernous sinus surgery, 523

Trochlear nerve
Reconstruction of the third through sixth cranial nerves during cavernous sinus surgery, 523

Tumor
The brow slide. A technique for the aesthetic treatment of eyebrow tumors, 120

Case records of the Massachusetts General Hospital (Case 21-1992), 388

In vivo gene transfer with retroviral vector-producer cells for treatment of experimental brain tumors, 390

Interferon alfa-2a therapy for life-threatening hemangiomas of infancy, 389

Meningiomas are not significantly associated with breast cancer, 658

Of sight and song, 527

Precision radiation therapy for optic nerve sheath meningiomas, 387

Sinonasal primitive neuroectodermal tumor arising in a long-term survivor of heritable unilateral retinoblastoma, 658

U

Ultraviolet
Present status of eyelid phototherapy. Clinical efficacy and transmittance of ultraviolet and visible radiation through human eyelids, 250

Scotopic spectral sensitivity of phakic and aphakic observers extending into the near ultraviolet, 656

Uvea
Uveal melanoma. Therapeutic consequences of doubling times and irradiation results. A review, 385

Uveitis
Risk factors for cyclosporine-induced nephropathy in patients with autoimmune diseases, 390
Uveitis and systemic disease, 114

V

Varicella-zoster
Acyclovir. A decade later, 793

Vincristine
Selective loss of optic nerve β-tubulin in vincristine-induced blindness, 791

Vision
Blind spots, 388
Phantom limbs, 391

Vision screening
Preschool vision screening in pediatric practice. A study from the Pediatric Research in Office Settings (PROS) Network, 391

Visual acuity
Case records of the Massachusetts General Hospital (Case 21-1992), 388

Visual field
Platelet aggregation, disc haemorrhage and progressive loss of visual fields in glaucoma. A seven year follow-up on glaucoma, 248
Postural disturbances due to homonymous hemianopic visual ataxia, 386

Visual system
The visual image in mind and brain, 661
Whiplash and its effect on the visual system, 790

Visual-evoked potential
Cortical blindness in children. Utility of flash VEPs, 386

Vitamin
Conjunctival impression cytology with transfer as a field-applicable indicator of vitamin A status for mass screening, 654

Vitreous
Terson's syndrome. A reversible cause of blindness following subarachnoid hemorrhage, 388

W

Women
A prospective study of cigarette smoking and risk of cataract surgery in women, 655

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Jackson Memorial Lecture
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Photoreceptor Outer Segments
Matsuo, Matsuo, Shiraga, Hosoda, Kawanishi, Watanabe, Ohtsuki

Interleukin-2 Receptor in Behçet's Disease
BenEzra, Maftzir, Kalichman, Barak

Corneal Topography
Maloney, Bogan, Waring

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Groos, Mannis, Brumley, Huntley

Orbital Meningoencephalocele
Terry, Patrinely, Anderson, Smithwick

Central Serous Choroidopathy
Scheider, Nasemann, Lund

Fluorescein Angiography and Giant Cell Arteritis
Siatkowski, Gass, Glaser, Smith, Schatz, Schiffman

Retinal Vasoconstriction After Laser Treatment
Gottfredsdóttir, Stefánsson, Jónasson, Gíslason

Early Revision of Blepharoptosis Correction
Dortzbach, Kronish

Ocular Changes During Accommodation
Shum, Ko, Ng, Lin

Fluorouracil Filtering Surgery Study
Fluorouracil Filtering Surgery Study Group

Corneal Endothelial Cells and Molteno Implant
McDermott, Swendris, Shin, Juzych, Cowden

Chordoma and Chondrosarcoma
Volpe, Liebsch, Munzenrider, Lessell

• PERSPECTIVES

Developmental Genes and Ocular Malformation Syndromes
Traboulsi

• LETTERS TO THE JOURNAL

Mitochondrial DNA deletions
Johns, Threlkeld, Miller, Hurko

Subconjunctival silicone oil
Hutchinson, Capone, Grossniklaus

Ophthalmic photodynamic therapy
Naoumidis, Tsilimbaris, Georgiades, Pallikaris

Granular, lattice, and macular dystrophies
Rodrigues, Kruth, Rajagopalan, Jones

***Mycobacterium chelonae* keratitis and ciprofloxacin**
Hwang, Biswell

Aqueous protein and intraocular lens power
Evans

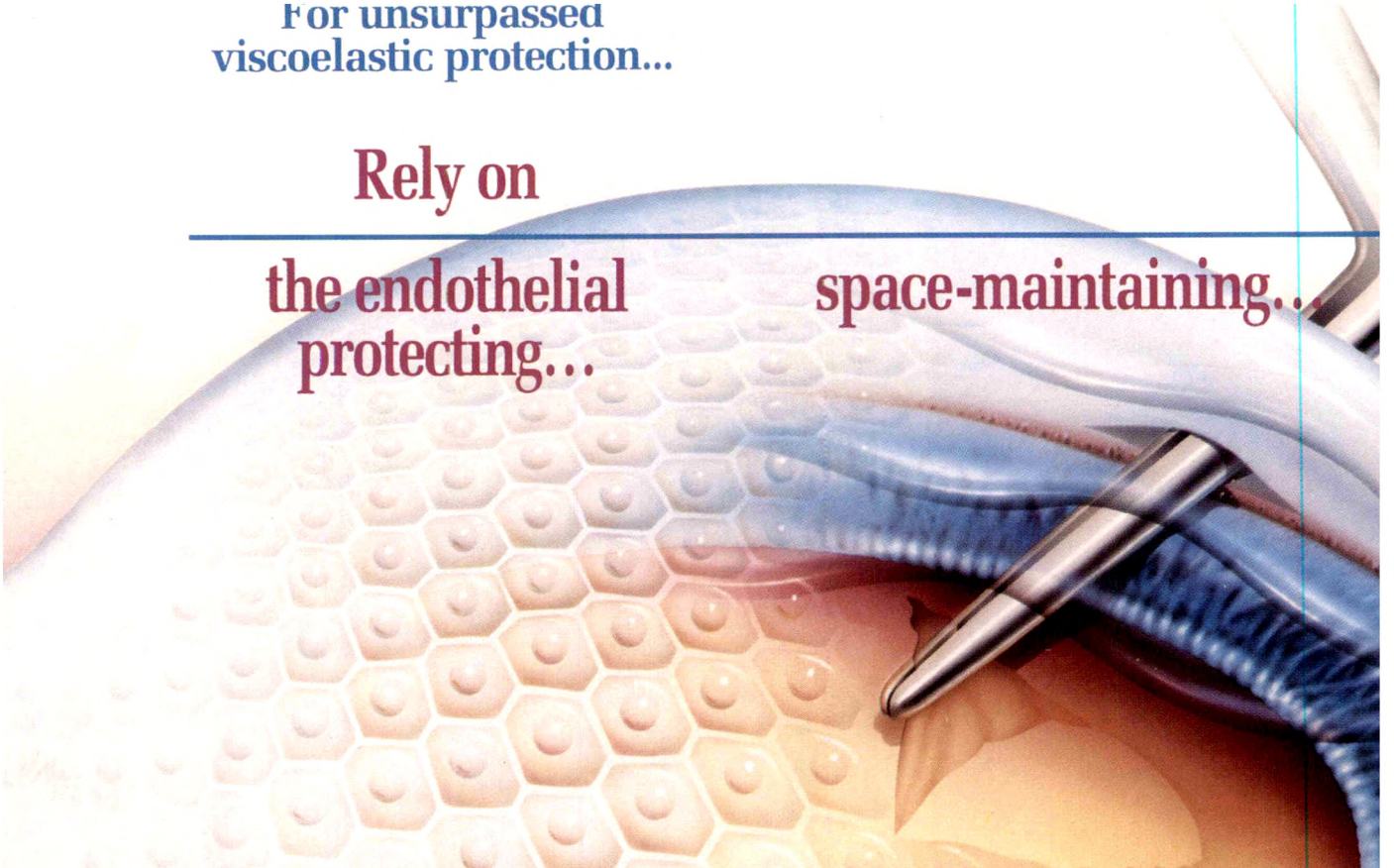
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AJO® AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 January 1993 Series 3, Vol. 115, No. 1

TABLE OF CONTENTS

ORIGINAL ARTICLES

Traction retinal detachment. XLIX Edward Jackson Memorial Lecture
Stephen J. Ryan 1

Photoreceptor outer segments in the aqueous humor of patients with atopic dermatitis and retinal detachment
Nobuhiko Matsuo, Toshihiko Matsuo, Fumio Shiraga, Akira Hosoda, Youko Kawanishi, Sei Watanabe, and Hiroshi Ohtsuki 21

Serum levels of interleukin-2 receptor in ocular Behçet's disease
David BenEzra, Genia Maftzir, Ina Kalichman, and Vivian Barak 26

Determination of corneal image-forming properties from corneal topography
Robert K. Maloney, Stephen J. Bogan, and George O. Waring III 31

Eyelid involvement in acanthosis nigricans
Erich B. Groos, Mark J. Mannis, Thomas B. Brumley, and Arthur C. Huntley 42

Orbital meningoencephalocele manifesting as a conjunctival mass
Andrew Terry, James R. Patrinely, Richard L. Anderson, and Walter Smithwick IV 46

Fluorescein and indocyanine green angiographies of central serous choroidopathy by scanning laser ophthalmoscopy
A. Scheider, J. E. Nasemann, and O.-E. Lund 50

Fluorescein angiography in the diagnosis of giant cell arteritis
R. Michael Siatkowski, J. Donald M. Gass, Joel S. Glaser, J. Lawton Smith, Norman J. Schatz, and Joyce Schiffman 57

Retinal vasoconstriction after laser treatment for diabetic macular edema
María Soffía Gottfredsdóttir, Einar Stefánsson, Fridbert Jónasson, and Ingimundur Gíslason 64

Early revision in the office for adults after unsatisfactory blepharoptosis correction
Richard K. Dortzbach and Jan W. Kronish 68

A biometric study of ocular changes during accommodation
Patrick Joi-Tsang Shum, Liang-Shi Ko, Chak-Lau Ng, and Shun-Ling Lin 76

Three-year follow-up of the Fluorouracil Filtering Surgery Study
The Fluorouracil Filtering Surgery Study Group 82

Corneal endothelial cell counts after Molteno implantation
Mark L. McDermott, Ronald P. Swendris, Dong H. Shin, Mark S. Juzych, and John W. Cowden 93

Neuro-ophthalmologic findings in chordoma and chondrosarcoma of the skull base
Nicholas J. Volpe, Norbert J. Liebsch, John E. Munzenrider, and Simmons Lessell 97

PERSPECTIVES

Developmental genes and ocular malformation syndromes
Elias I. Traboulsi 105

LETTERS TO THE JOURNAL

Multiple mitochondrial DNA deletions in myoneuro-gastrointestinal encephalopathy syndrome. *Donald R. Johns, Anisa B. Threlkeld, Neil R. Miller, and Orest Hurko,* **108. Subconjunctival silicone oil after vitreoretinal surgery.** *Amy K. Hutchinson, Antonio Capone, and Hans E. Grossniklaus,* **109. A diode laser mounted on a slit lamp for ophthalmic photodynamic applications of phthalocyanine.** *Leonidas P. Naoumidis, Miltiades K. Tsilimbaris, Anthimos Georgiades, and Ioannis G. Pallikaris,* **111. Unesterified cholesterol in granular, lattice, and macular dystrophies.** *Merlyn M. Rodrigues, Howard S. Kruth, Sankaran Rajagopalan, and Kelly Jones,* **112. Ciprofloxacin therapy of *Mycobacterium chelonae* keratitis.** *David G. Hwang and Roderick Biswell,* **114. Aqueous humor protein and intraocular lens powers.** *Lawrence S. Evans,* **116. Distinguishing compensatory head turn from gaze palsy in children with unilateral oculomotor or abducens nerve paresis.** *William J. Benevento and Lawrence Tychsen,* **117. Tricholemmal carcinoma of the eyelid.** *John R. Dailey, Klaus F. Helm, and Stuart H. Goldberg,* **118.**

CORRESPONDENCE

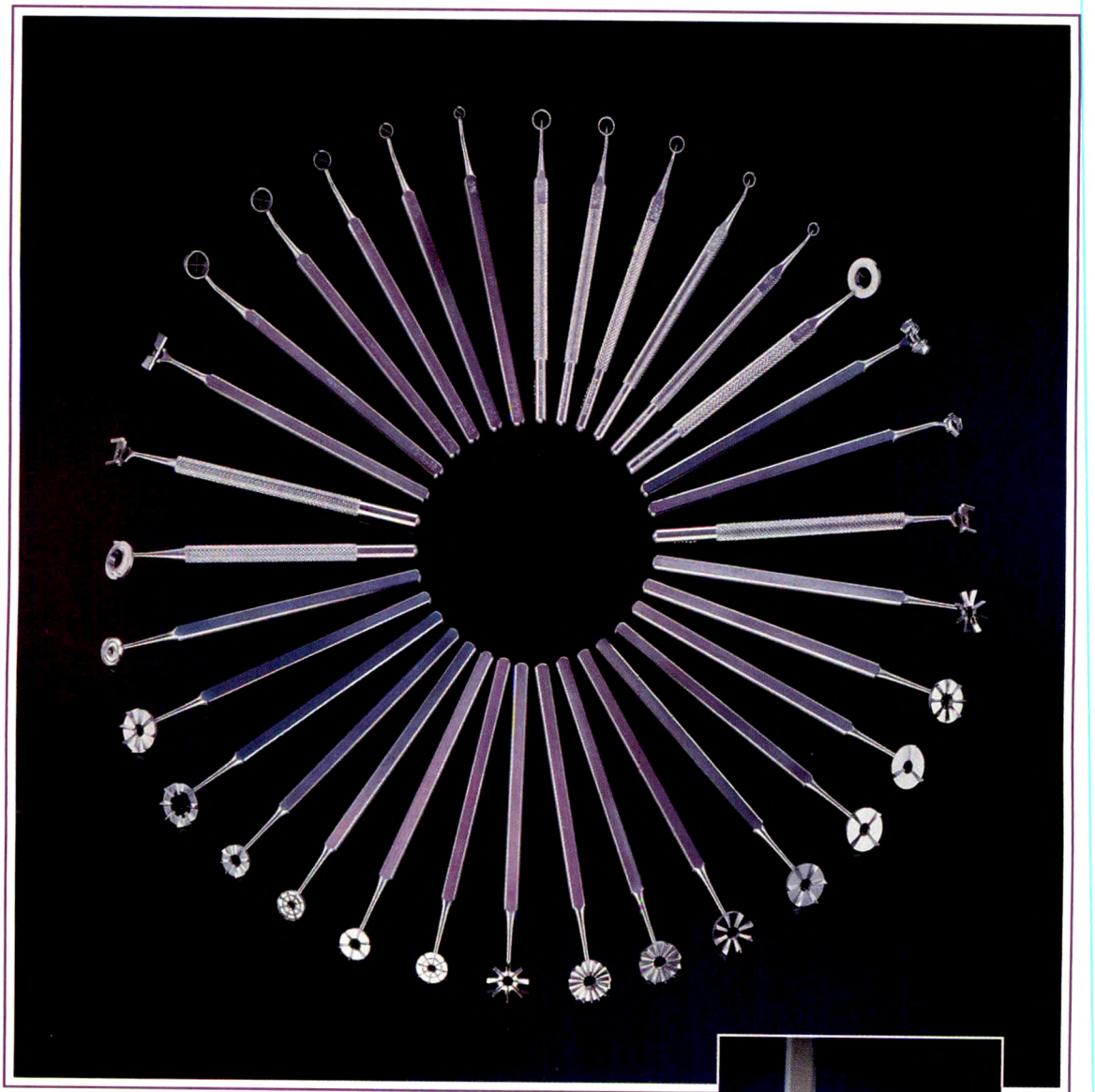
Meibomian gland function and giant papillary conjunctivitis. *Salim I. Butrus and Andrew I. Rabinowitz,* **119. Reply.** *W. D. Mathers and M. Billborough,* **120. Meibomian gland function and giant papillary conjunctivitis.** *Roy S. Rubinfeld and Neil F. Martin,* **120. Clinical and histopathologic changes in the host cornea after epikeratoplasty for keratoconus.** *Herbert E. Kaufman and Marguerite B. McDonald,* **121. Reply.** *Merlyn Rodrigues, Verinder Nirankari, Sankaran Rajagopalan, Kelly Jones, and James Funderburgh,* **122. Visual outcome after penetrating keratoplasty with double continuous or combined interrupted and continuous suture closure.** *Louis J. Girard,* **123. Reply.** *K. K. Assil, S. R. Zarnegar, and D. J. Schanzlin,* **124. Vagal responses to adjustable sutures in strabismus correction.** *Burton J. Kushner,* **124. Reply.** *H. S. Eustis, C. C. Eisworth, and D. R. Smith,* **125. Superior rectus muscle overaction after cataract extraction.** *W. Bruce Wilson,* **126. Reply.** *M. R. Grimmet and S. R. Lambert,* **127.**

BOOK REVIEWS

The History of Ophthalmology, vol. 11. The Reform of Ophthalmology, part 1-B, by J. Hirschberg

(Table of Contents continued on Advertising Page 8)

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ISSN 0002-9394 January 1993 Series 3, Vol. 115, No. 1

TABLE OF CONTENTS *(continued from Advertising page 6)*

(Translated by F. C. Blodi). *Reviewed by Mark J. Mannis,* **129. The History of Ophthalmology, vol. 11. The Reform of Ophthalmology, part 1-C, by J. Hirschberg (Translated by F. C. Blodi).** *Reviewed by Mark J. Mannis,* **129. Age-Related Macular Degeneration. Principles and Practice (Edited by G. Robert Hampton and Philip T. Nelson).** *Reviewed by Thomas G. Chu,* **130. Adler's Physiology of the Eye, ed. 9 (Edited by William M. Hart, Jr.).** *Reviewed by William Gruzensky,* **130. Ophthalmic Toxicology (Target Organ Toxicology Series) (Edited by George C. Y. Chiou), 131. Ophthalmology Oral History Series. A Link with our Past. An Interview with Paul Boeder (Interviewed by Sally Smith Hughes), 131. Pediatric and Adolescent Endocrinology, vol. 22. Structural and Functional Abnormalities in Subclinical Diabetic Angiopathy (Edited by B. Weber, W. Burger, and T. Danne), 132.**

ABSTRACTS 133

NEWS ITEMS 141

CLASSIFIEDS . . . . . Begins on Advertising 46

COPYRIGHT TRANSFER . . . . . Advertising 32

INSTRUCTIONS TO AUTHORS . . . . . Advertising 35

PRODUCTS AND SERVICES . . . . . Begins on Advertising 40

ADVERTISING INDEX . . . . . Advertising 49

Traction Retinal Detachment
XLIX Edward Jackson Memorial Lecture

Stephen J. Ryan, M.D.

This review had two main objectives. The first goal was to attempt to define a final common pathway for traction retinal detachment. To illustrate this, I considered the following three common clinical entities: penetrating ocular trauma, proliferative vitreoretinopathy, and proliferative diabetic retinopathy. My second goal was to emphasize the role of research in developing a rational approach to treatment. To illustrate the second goal, I reviewed the contributions from three realms of research—laboratory, animal, and clinical research—examining their interactions and considering their roles in our current understanding and management of these clinical entities.

THE JACKSON LECTURE is widely recognized as one of the most prestigious lectures in ophthalmology because it honors the memory of Edward Jackson, who was one of the preeminent ophthalmologists of his day and the man responsible for the concept of continuing medical education. The list of ophthalmologists who have given the Jackson Lecture is a virtual "Who's Who" in ophthalmology, and I am deeply honored to have been selected to make this presentation.

The goal of this review is twofold. The first is to define a final common pathway for traction retinal detachments (Fig. 1). I consider three common clinical entities: penetrating ocular trauma, proliferative vitreoretinopathy, and proliferative diabetic retinopathy. My second goal is to emphasize the role of research in developing a rational approach to treatment. To illustrate this goal, I demonstrate how three realms of research, laboratory, animal, and clinical research, interact to contribute to our understanding and management of these clinical entities (Fig. 2).

Retinal detachment remains a leading cause of blindness, even though considerable progress has been made in understanding its pathogenesis, including the pathoanatomy (both normal structure and the pathologic changes that transpire) and the pathobiologic characteristics (altered function). Although much work remains to be done, retinal specialists can take pride in the many advances that have been made over the last 20 years.

From the initial observation by Jules Gonin, in 1921, of the importance of the retinal hole, to the development of the binocular indirect ophthalmoscope, to refinement of scleral buckling techniques by Charles Schepens, to the use of the plombage by Custodis, to introduction of vitrectomy by Machemer, and, more recently, to the use of light and heavy oils for retinal tamponade, steady progress has been made in the treatment of traction retinal detachment. This chronology of progress has been well reviewed in the Jackson Memorial Lectures given by Robert Machemer in 1984[1] and by Thomas Aaberg in 1988.[2]

The pathogenesis of traction detachment has many similarities in penetrating ocular trauma, proliferative vitreoretinopathy associated with rhegmatogenous retinal detachment, and proliferative diabetic retinopathy, although each has its own peculiar pathoanatomic and pathobiologic aspects. Our understanding of the pathogenesis of traction retinal detachment is based on knowledge of the wound-healing re-

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From the Department of Ophthalmology, University of Southern California School of Medicine, and the Doheny Eye Institute, Los Angeles, California. Presented at the 1992 American Academy of Ophthalmology annual meeting, Dallas, Texas, Nov. 9, 1992.

Reprint requests to Stephen J. Ryan, M.D., Doheny Eye Institute, 1450 San Pablo St., Los Angeles, CA 90033.

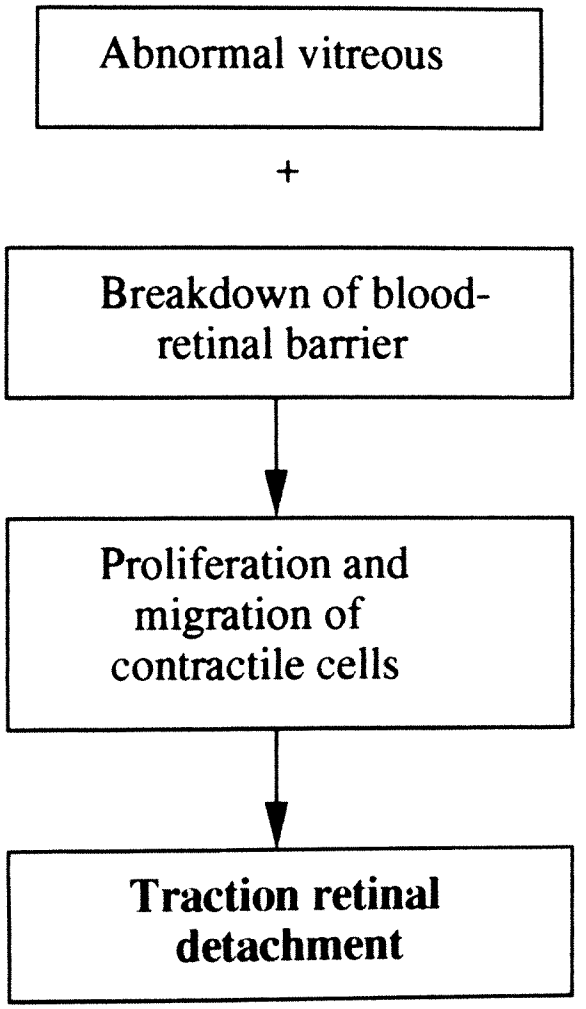


Fig. 1 (Ryan). Common pathway for pathogenesis of traction retinal detachment in three different situations: trauma, proliferative vitreoretinopathy, and proliferative diabetic retinopathy.

sponse that characterizes these conditions. Vitreoretinal relationships, and especially the relationship of the vitreous base to the ora serrata, render the process of wound healing, which is beneficial elsewhere in the body, so devastating in the eye, where wound healing can lead to traction detachment. This is most clearly seen after penetrating ocular injury. Proliferative vitreoretinopathy associated with rhegmatogenous retinal detachment also has features of the wound-healing response that lead to traction detachment. In diabetic retinopathy, the vitreoretinal relationship in the more posterior retina and the process of neovascularization leads to and complicates the wound-healing response, resulting in traction retinal detachment.

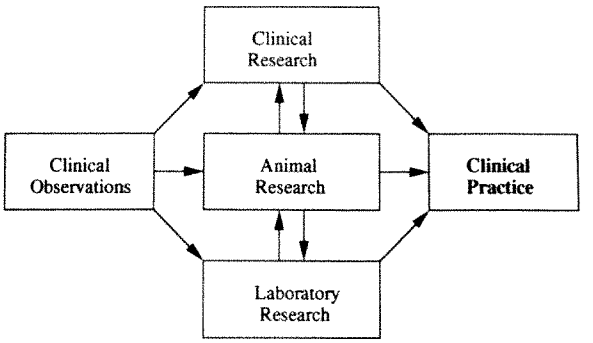


Fig. 2 (Ryan). Flow chart depicting interaction of three realms of research: clinical, animal, and laboratory research.

The common feature in all these conditions is a breakdown of the blood-retinal barrier that is associated with or leads to an inflammatory response, including an infiltration of leukocytes (Fig. 1). Serum factors that leak from the vessels and cytokines released by the leukocytes, particularly macrophages and monocytes, cause proliferation and migration of retinal cells that form cellular membranes, the contraction of which exerts tractional forces on the retina. When these forces, which we have actually measured, overcome the normal forces of adhesion that bind the retina to the retinal pigment epithelium, traction retinal detachment occurs.

Final Common Pathway For Traction Retinal Detachment

Step 1—An underlying disease process or an inciting event leads to an inflammatory response that affects the posterior segment of the eye.

Step 2—The resultant breakdown of the blood-retinal barrier, combined with abnormal vitreous, initiates the wound-healing response.

Step 3—The migration and proliferation of cells within the posterior segment is a key element.

Step 4—When these cells attain a critical mass such that their force of contraction exceeds the forces of attachment of the sensory retina, then traction retinal detachment occurs.

Step 5—When the traction detachment begins, the detachment itself leads to further breakdown of the blood-retinal barrier and inflammation that leads to acceleration of the process with further retinal detachment in a vicious circle.

This process, including the five steps listed

previously, varies with the inciting event or disease process, or both. We conceive of a life cycle in which, initially, serum-derived products and circulating inflammatory cells predominate; this initial stage is followed by migration and proliferation of cells, including retinal pigment epithelial cells, glial cells, fibroblasts, myofibroblasts, endothelial cells migrate, proliferate, and other cells that contract and lay down extracellular matrix, including collagen. In the end stage of untreated traction detachment, there is frequently prominent new collagen and extracellular matrix, but there are few inflammatory cells or contractile cells.

Penetrating ocular trauma, proliferative vitreoretinopathy, and proliferative diabetic retinopathy are three diseases that best illustrate this final common pathway that leads to traction retinal detachment.

Penetrating Ocular Trauma

Trauma is a discrete inciting event that fundamentally alters a previously normal eye. The wound-healing response in the eye is the same as elsewhere in the body. This wound-healing process is, in effect, the final common pathway that leads to traction detachment. Before understanding this pathogenesis from animal research and early clinical experience with vitrectomy, ophthalmologists focused on the final outcome only, that is, traction retinal detachment in its end-stage appearance.

The first large retrospective study of ruptured globes was conducted by Cherry[3] at the Wilmer Eye Institute between 1952 and 1970. He found that only 6% of the injured eyes had a final visual acuity of 5/200 or better (considered to be ambulatory vision). This poor outcome contrasts with that described in another retrospective study of a series of patients who had similar ocular injuries that were treated with more modern surgical techniques at the same institution between 1970 and 1981. Of these patients, 31% obtained visual acuity of 5/200 or better.[4] The advent of microsurgery in the 1960s, which led to a better approximation of ocular wounds, and the development of vitrectomy techniques in the 1970s permitted more successful repair of posterior segment wounds and resulted in a dramatic improvement in the prognosis of penetrating ocular injuries. This improvement is not the result of technology alone, but is, I believe, attributable in large part to the development of treatment based on better understanding of the wound-healing response to penetrating ocular trauma (Fig. 2).

Numerous histologic studies in the 1950s and 1960s of eyes enucleated after severe penetrating ocular trauma showed an abundance of collagenous fibrocellular tissue that replaced the normal vitreous and that caused a traction retinal detachment. It was widely believed that the collagenous tissue per se was able to contract and to pull the retina forward literally, thereby causing detachment. Leading ophthalmic pathologists described this mechanism of collagen contraction in their papers and presentations, based on their histologic studies of enucleated eyes. Philip Cleary and I emphasized the importance of cellular contraction in our series of experiments.

In the late 1970s, Philip Cleary and I commenced our pathobiologic studies of penetrating pars plana injury in a rabbit and primate model. In the primate, an 8-mm incision was made through the sclera at the pars plana, resulting in prolapse of vitreous gel.[5-8] There was no damage to the retina or crystalline lens. The wound was closed by microsurgical techniques. We found that retinal detachment did not occur after saline injection or injection of ground lens material from another monkey into the vitreous cavity of these monkeys.[9,10] However, 73% of the wounded monkey eyes developed traction retinal detachment after injection of 0.5 ml of blood into the vitreous cavity (Fig. 3). Therefore, it is the combination of abnormal, or in this case injured, vitreous and the breakdown of the blood-retinal barrier, or in this case the injection of blood, that initiates the final common pathway (Fig. 1) that leads to traction retinal detachment (Fig. 4). Some of these proliferating cells lay down collagen, which further immobilizes the detached retina (Fig. 5).[11] It must be emphasized that the detachment is produced by contractile cells, including myofibroblasts in the vitreoretinal membranes.

Another ocular response to trauma is posterior vitreous detachment (Fig. 6), which determines the nature and location of the vitreous scaffolding on which cells can proliferate. Normally, the posterior cortical vitreous is on and tightly adherent to the inner limiting membrane, especially in the region of the vitreous base.[12,13] After severe penetrating ocular trauma, however, detachment of the posterior vitreous base is a common phenomenon. When this occurs, the cleavage is most commonly between the vitreous cortex and the internal limiting membrane of the retina. Cleavage can occur within the outer cortical vitreous, however.[14]

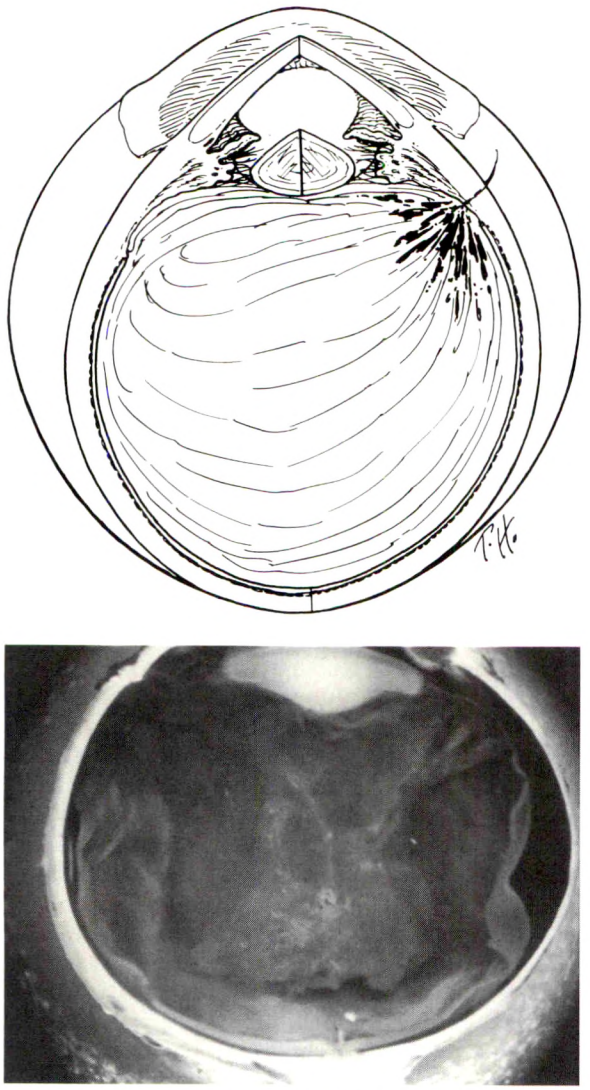


Fig. 3 (Ryan). Top, Injection of 0.05 ml of blood into the vitreous cavity after penetrating pars plana injury, shown diagrammatically. Bottom, Experimental primate model.

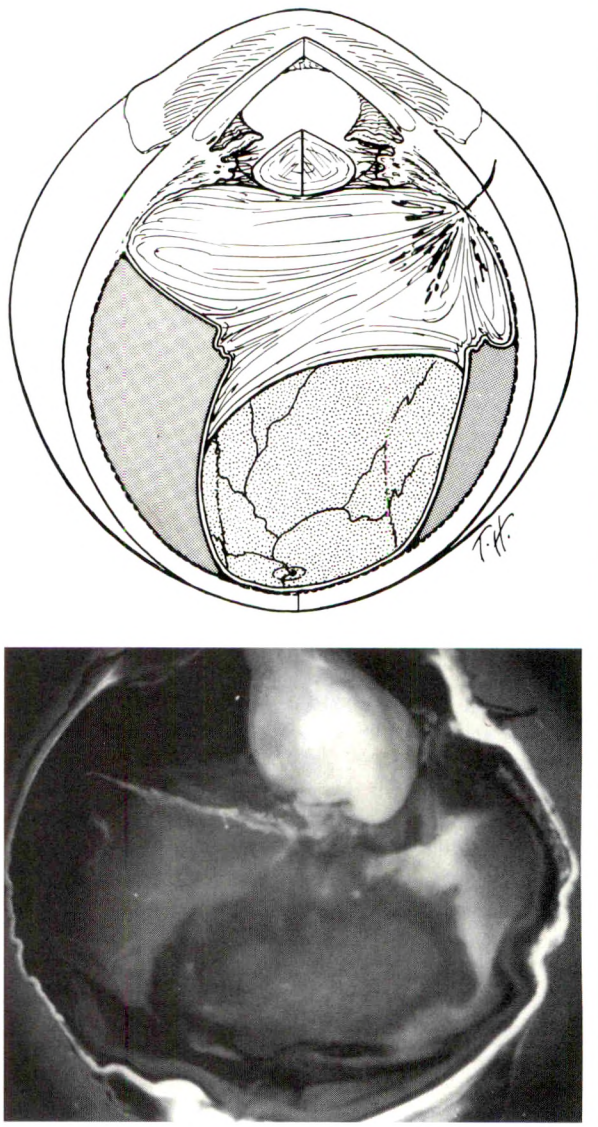
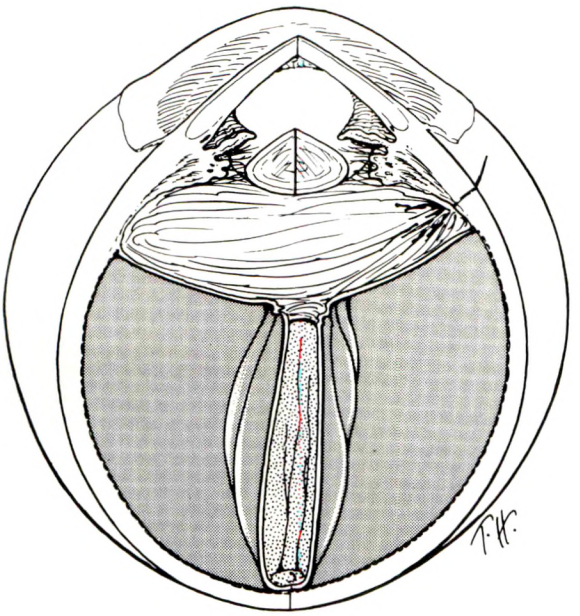


Fig. 4 (Ryan). Top, Combination of penetrating ocular injury and injection of blood initiates a final common pathway that leads to anteroposterior, perpendicular, and circumferential tractional forces. Bottom, Resultant traction retinal detachment.

Therefore, the degree to which cortical fibers remain on the retinal surface varies.

The pathogenesis of posterior detachment after penetrating trauma is not known with certainty. It is known, however, that breakdown of the blood-retinal barrier results in leakage of serum components and migration of macrophages into the vitreous cavity. The macrophages are thought to release enzymes that disrupt the vitreous gel, and perhaps the vitreoretinal bond, and this may lead to a posterior vitreous detachment. Serum components that may be important in this interaction include fibronectin, laminin, and integrin.[15]

In the primate model of traumatic traction retinal detachment, thick cellular membranes were observed in the peripheral and posterior retina after injury.[16] Ultrastructural studies indicated that these membranes consisted primarily of fibroblasts, myofibroblasts, and glial cells.[17] Myofibroblasts have ultrastructural features in common with both fibroblasts and



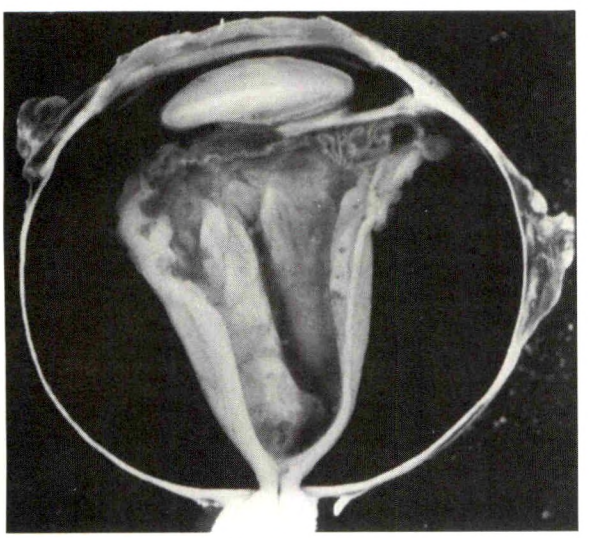


Fig. 5 (Ryan). Top, Further traction and secretion of collagen by proliferating cells causes a total, funnel-shaped traction retinal detachment with immobilization of the detached retina shown diagrammatically. Bottom, Experimental primate model.

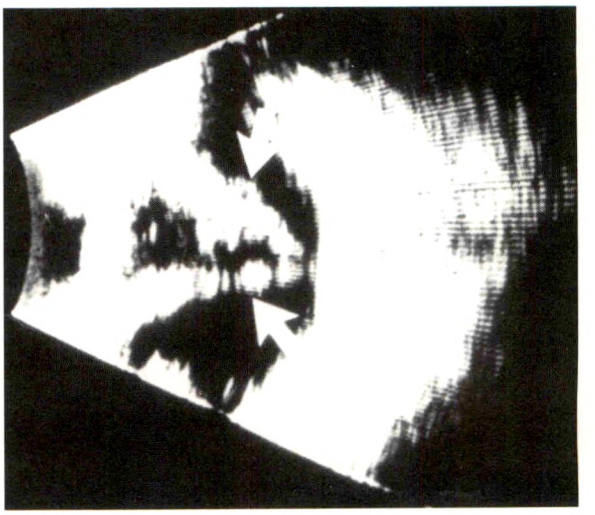


Fig. 6 (Ryan). Total posterior vitreous detachment (arrows) is well-delineated by ultrasonography ten days after penetrating ocular injury.

smooth muscle cells, although the origin of this cell type is unclear. Fibroblasts can be derived from the systemic circulation, from the adventitia of small vessels, or from cells at the edge of the wound. Myofibroblasts can be derived from fibroblasts or from multipotential stem cells.[18] Various cells within the eye, such as glial cells, retinal pigment epithelial cells, and macrophages, may be capable of metaplasia in response to environmental changes, and thus could function like myofibroblasts in terms of their ability to contract.[19,20]

The development of a reproducible primate model of posttraumatic traction retinal detachment facilitated the testing of therapeutic methods such as pars plana vitrectomy. The main role of vitrectomy performed within two weeks of the injury is to remove the blood and other pathologic stimulants of the wound-healing response. By removing these stimulants, the wound-healing process may be aborted. Vitrectomy also removes the vitreous scaffold, including the proliferating cells and serum products. The removal of the stimulants reduces the wound-healing response and limits the extent of membrane formation and subsequent traction retinal detachment.[16] Because a posterior vitreous detachment, to one extent or another, occurs within two weeks after the penetrating ocular injury, pars plana vitrectomy was found to be most effective in a pig model when performed in the second week after injury.[21] The more complete the removal of the vitreous gel, the less the chance of developing a traction retinal detachment. Complete removal of the vitreous is not possible, however, especially at the vitreous base. Therefore, the added use of an encircling scleral buckle to support the vitreous base affords the greatest chance of a successful result.

Even as the animal studies were being performed, their limitations became evident. Although clinical and ultrastructural changes could be demonstrated, the biochemical interaction that resulted in these changes could not be studied. To this end, in the last ten years much research has been devoted to identifying the biochemical stimuli for intraocular proliferation. Recent studies have suggested that the retinal pigment epithelial cells, through the production of cytokines and extracellular matrix and the development of immune competency, also regulate ocular wound healing.[22-25]

The role of immediate pars plana vitrectomy to prevent the toxic effects or endophthalmitis caused by an intraocular foreign body is well recognized. Although the animal research previously cited does support the role of vitrectomy in such conditions, a large, multicenter clinical study such as the work done thus far by the Diabetic Retinopathy Study Vitrectomy group has not been done on trauma. Consequently, our standard of clinical practice is based largely on the results of animal research and, to a more limited extent, on laboratory research. Several clinical studies have contributed greatly to define the role of vitrectomy after penetrating ocular injury. The results, however, must remain inconclusive because of the inherent variability of ocular trauma.

Another controversy over the management of penetrating ocular trauma concerns the timing of vitrectomy. Some experienced vitreoretinal surgeons favor operating within the first 48 to 72 hours.[26] Surgery at this time is thought to decrease the risk of intraocular proliferation by preventing the development of severe inflammatory changes. Additionally, early vitrectomy may improve the prognosis by permitting examination of the fundus, with immediate repair of obvious retinal tears and detachment. Other vitreoretinal surgeons, however, influenced by animal research, prefer delaying surgery until after 72 hours.[27-30] This delay allows for more accurate diagnostic examination of the eye, including detailed ultrasonography and electrophysiologic studies. The delay may also allow for better visualization by the clearing of the ocular media. Most importantly, animal research has shown that spontaneous separation of the posterior hyaloid face often occurs during this period, making the excision of the posterior cortical vitreous easier and less hazardous. An ultrasonogram of an eye with posterior vitreous detachment is shown in Figure 6, and the diagram of Figure 7 shows the vitreous

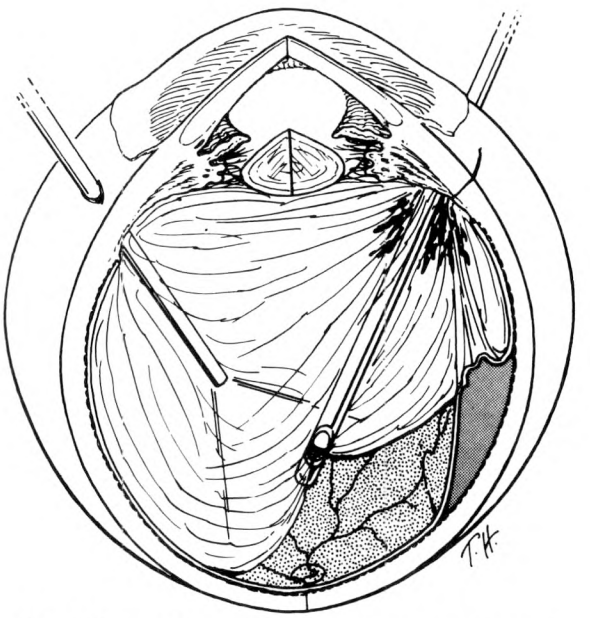


Fig. 7 (Ryan). Pars plana vitrectomy done approximately ten days after penetrating ocular injury is aided by a partial or total posterior vitreous detachment.

cutter between the posterior hyaloid and the detached retina.[14] Additionally, when early vitrectomy is performed, severe vitreous hemorrhage caused by uveal congestion associated with the initial penetrating injury is a distinct possibility. Although rare, when this complication occurs intraoperatively, it can be a disaster. Delayed surgery, therefore, may decrease the risk of such uncontrollable intraoperative hemorrhage.[30]

Yet another controversy in the management of penetrating ocular injuries concerns the use of a prophylactic scleral buckle. The two reasons cited for prophylactic scleral buckle are the difficulty in visualizing the peripheral retina in a traumatized eye with residual vitreous hemorrhage, and the desire to support the vitreous base against the possibility of later vitreous traction. Application of a circumferential scleral buckle may prevent a vitreous base traction detachment (Fig. 8).[31,32] Animal research does support the argument that residual cortical vitreous is present at the vitreous base, no matter how thorough the vitrectomy (Fig. 9). Moreover, animal research has also shown that this residual vitreous provides the basis for cells to contract and cause a retinal detachment caused by foreshortening of the retina, particularly the peripheral portion of the retina.[14] Therefore, to prevent such a complication,



Fig. 8 (Ryan). Broad circumferential scleral buckle over the vitreous base may prevent or delimit a partial anterior retinal detachment caused by traction of residual vitreous at the vitreous base.

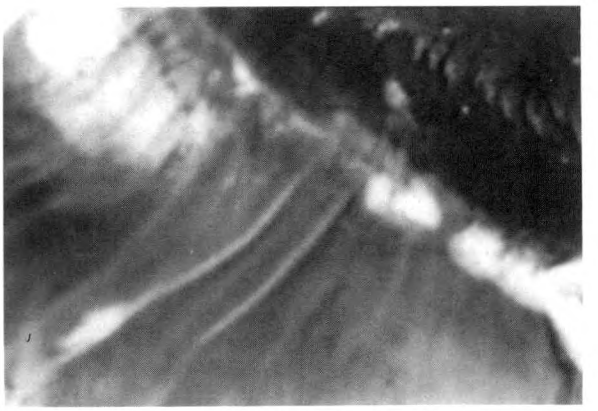


Fig. 9 (Ryan). In the absence of a circumferential scleral buckle, contraction of the peripheral residual vitreous may cause an anterior traction retinal detachment, as seen in this gross photograph of a human eye.

placement of a low to medium scleral buckle to support the vitreous base is indicated. Although several small clinical studies have supported this hypothesis,[31,32] no well-controlled prospective study exists.

An earlier controversy concerned the proper role of cryotherapy. Previously, cryotherapy was applied to the edges of a scleral rupture or laceration in hopes of preventing a rhegmatogenous retinal detachment secondary to the discontinuity of the retina at the edge of the laceration. Clinical experience with vitrectomy and animal studies improved understanding of the wound-healing response, including inflammation, as the fundamental problem. A major benefit from vitrectomy is the removal of blood and other factors that stimulate the inflammatory response.[33] Cryotherapy, however, causes an inflammatory response. Accordingly, prophylactic cryotherapy to scleral wound edges should be avoided, except in the presence of a functional retinal hole, which produces a rhegmatogenous component to the detachment, in addition to traction.

The importance of a well-organized, multicenter prospective study on penetrating ocular injuries cannot be overstated. It is precisely because of a lack of such a study that many important and immediate questions remain unanswered. Moreover, in lieu of such a study, ophthalmologists rely on the results of animal research, which always have the potential of being inapplicable to humans. Therefore, it is the challenge of the clinical ophthalmologist to assess objectively the results and limitations of animal research, laboratory research, and small, poorly controlled, inconclusive, and often conflicting clinical series.

Proliferative Vitreoretinopathy

The second of the illustrative trio of diseases characterized by traction retinal detachment is the clinical entity known as proliferative vitreoretinopathy. The pathway described, initial breakdown of the blood-retinal barrier with inflammation and the release of extracellular factors that lead to the migration and proliferation of cells to form contractile membranes, and which ultimately results in tractional forces that detach the retina, is evident in this condition as well (Fig. 1).[34,35]

The most common reason for failure of retinal reattachment is proliferative vitreoretinopathy—an excessive wound-healing response to rhegmatogenous retinal detachment.[36] Clinical research and, to a lesser extent, laboratory research have had important roles in the development of effective therapeutic strategies for proliferative vitreoretinopathy (Fig. 2). The spectrum of clinical research for proliferative vitreoretinopathy has ranged from independent innovation to prospective clinical trials, in both the United States and Europe.

Because of the large number of investigators

working on proliferative vitreoretinopathy, the need arose for a standardized classification of the pathoanatomy. In 1983, the Retina Society proposed such a classification based on the extent and severity of proliferative membranes as defined by the number of quadrants involved and the shape of the detachment.[37] Experience has shown that perhaps a more relevant pathoanatomic description of this disease should be based on the differentiation between anterior and posterior proliferative elements, as emphasized by vitreous surgeons involved with the Silicone Oil Study.[2,38,39] A new classification system that reflects this insight and emphasizes anterior as well as posterior proliferative vitreoretinopathy was reported in 1989[40] and updated in 1991.[41]

The earliest stages of proliferative vitreoretinopathy, grade A and grade B, remain unchanged in this new classification. Grade A denotes the earliest recognizable changes, that is, pigment clumps in the vitreous matrix resulting from the proliferation of pigmented cells. Grade B is defined by the presence of wrinkling of the inner retinal surface and retinal breaks with rolled or irregular edges. The new system then diverges from the old and differentiates between anterior and posterior disease (Figs. 10 and 11) and, for the first time, a description of the type of contraction is used to define the process. Posterior disease can be described as either focal or diffuse; focal disease is manifested by starfolds posterior to the vitreous base, and diffuse disease refers to confluent starfolds in the same location.

Anterior proliferative vitreoretinopathy is subdivided on the basis of the direction of pull of the contractile elements. Circumferential disease refers to contraction along the posterior edges of the vitreous base with a central displacement of the retina and stretching of the peripheral retina; anterior displacement refers to contraction in an anteroposterior direction, resulting in peripheral retinal troughs and stretched ciliary processes, with or without iris retraction. Subretinal disease denotes membranes beneath the retina, and may be anterior, posterior, or both.

Current therapeutic strategies for proliferative vitreoretinopathy are based on the observations of investigators, including clinicians with diverse backgrounds. Taking the lead from vitreoretinal surgeons who have described the natural course of this disease, molecular and cellular biologists are working to define the basic mechanisms of this process and how it

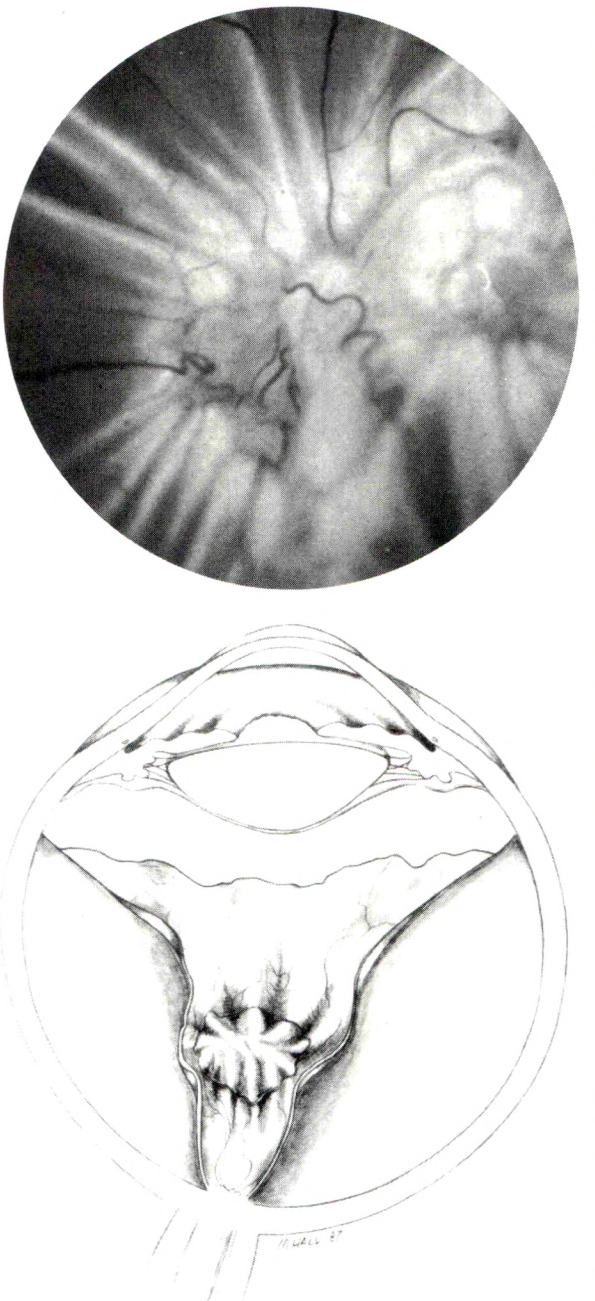


Fig. 10 (Ryan). Posterior proliferative vitreoretinopathy. Top, Fundus photograph of confluent posterior starfolds. Bottom, Contraction associated with a single starfold.

relates to other intraocular proliferative diseases.[25,42-45] As stated previously, proliferative vitreoretinopathy is a consequence of the wound-healing response to rhegmatogenous retinal detachment. As such, it follows the final common pathway that leads to traction retinal de-

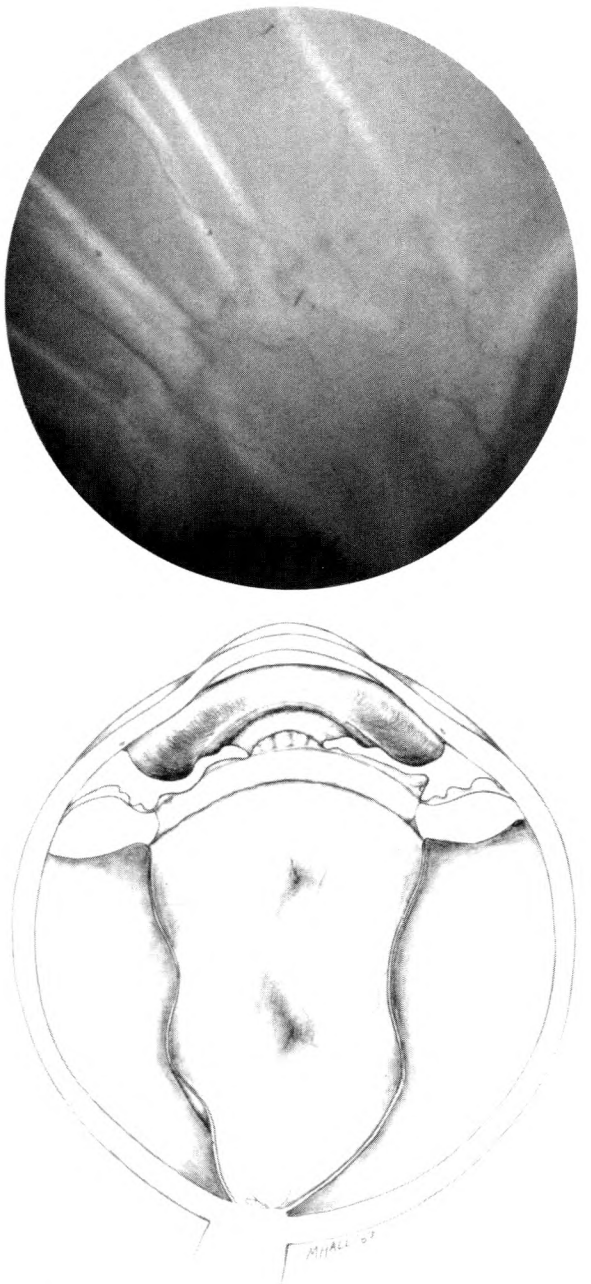


Fig. 11 (Ryan). Anterior proliferative vitreoretinopathy. Top, Fundus photograph of circumferential traction resulting in radial retinal folds. Bottom, The perpendicular forces of contraction that result in folds.

tachment in trauma. The triggering event appears to be a breakdown of the blood-retinal barrier, which leads to the exposure of previously quiescent retinal cells to bloodborne inflammatory cells, including polymorphonuclear cells and macrophages.[46,47] In the presence of at least eight extracellular factors that function alone or in concert, a remarkable differentiation and proliferative process takes place.[25,48-53] Retinal pigment epithelial cells, fibroblasts, and glial cells begin to divide and migrate. These same cells, in turn, produce their own extracellular factors and influence each other in what is, as yet, a poorly understood scenario. What is understood, however, is that cells organize and differentiate to form a critical mass of connective tissue associated with extracellular matrix proteins.[54,55] As part of this final common pathway, fibroblasts differentiate into myofibroblastlike cells and take on many of the contractile aspects of smooth muscle cells. Vascular endothelial cells proliferate, migrate, and mount an angiogenic response. Many different cells elaborate an extracellular matrix composed of proteins, including fibronectin, laminin, and types I, II, and IV collagen.[55] These combine to form a scaffold, along which contractile cells grow and are attached to the retina. Eventually, the contractile forces exceed the normal forces of retinal attachment, and further detachment occurs.[56,57]

With the in vitro data that have defined the types of cells and extracellular factors important in this process, several investigators have attempted to produce animal models of this disease. Several imperfect models have been generated by the intravitreal injection of fibroblasts or activated macrophages, but these animal models circumvent the crucial first steps of cellular transformation and proliferation.[58,59] An ideal model would be one in which the retina of an experimental animal might somehow be stimulated to produce the regulators, both stimulatory and inhibitory, of the wound-healing process. Such a model would allow investigators to answer questions regarding the spatial and temporal expression of these extracellular factors. In the future, transgenic animals, whose genes for these extracellular factors are controlled by inducible promoters, may be useful. Such models might also serve as a means to evaluate medical therapy for proliferative vitreoretinopathy.

Insights gained through laboratory studies are currently being translated into collaborative therapeutic trials. The concept that the proliferative response might be blocked by antimetabolites has led investigators to study the effects of antiproliferative drugs on the development of intraocular membranes.[60-62] A multicenter trial to study the effectiveness of

infusion of daunorubicin during vitrectomy for proliferative vitreoretinopathy is underway in Europe (P. Wiedemann, M.D., and K. Heinemann, M.D., written communication, Sept. 7, 1992). Approaches such as these, which combine vitreoretinal techniques with new knowledge of pathobiologic characteristics of cells, will be crucial to reduce the morbidity associated with proliferative vitreoretinopathy.

Great progress in the treatment of proliferative vitreoretinopathy is seen in surgical innovation, involving the multicenter studies performed thus far by the Silicone Study Group. The standard of care has progressed from simple buckling techniques to vitrectomy with membrane segmentation endolaser treatment, to the use of gas or, more recently, heavy liquids intraoperatively to achieve retinal tamponade.[63-67]

Cibis and associates[68] introduced the use of intraocular silicone in 1962. Although this quickly fell into disfavor in the United States, investigators in Europe continued to study its value in vitreoretinal surgery, and in 1975, Scott[69] clearly demonstrated the therapeutic value of silicone oil. Used in conjunction with vitrectomy, he was able to reattach retinas that would previously have been irreparable. In 1985, the Silicone Study[70] commenced to evaluate silicone oil and gas and to compare their relative effectiveness as intraocular tamponade adjuncts for retinal reattachment.

As a randomized prospective trial, the Silicone Study was designed to provide reliable, unbiased information about the effectiveness of silicone oil as compared with sulfur hexafluoride (SF_6) or perfluoropropane (C_3F_8) gas in retinal reattachment. Several variables were examined, including functional and anatomic success in reattachment, complication rates, and outcomes between eyes that had previously undergone vitrectomy and eyes without previous vitrectomy.

This study clearly demonstrated a better outcome in eyes treated with silicone oil than in eyes treated with SF_6 gas, as measured by the percentage of patients in whom visual acuity improved to 5/200 or better. No marked difference was noted between eyes treated with oil or with C_3F_8 gas.[63,64] Additionally, it was this study that led to the critical differentiation between anterior and posterior tractional elements and to the development of a classification system to reflect this insight. The Silicone Study is an example of a clinical trial, much like the Diabetic Retinopathy Vitrectomy Study, that provides a forum for the development of guidelines for the surgical management of complicated retinal detachments. Only through large-scale, collaborative studies such as these can crucial surgical observations be reliably made. I am sure that the future will see an extension of such collaborative studies to include not only vitreoretinal surgeons, but also pathologists and molecular biologists.

Proliferative Diabetic Retinopathy

Diabetic retinopathy is the leading cause of blindness in the United States of persons aged 60 years or younger. The systemic microangiopathy, characteristic of diabetes, is manifested in the eyes. Typically, an ophthalmologist will focus on the vascular abnormalities, including leakage, hemorrhage, and capillary loss with resultant hypoxia that leads to neovascularization. With separation of the abnormal vitreous and neovascularization, the resultant inflammatory response contributes to the wound-healing response, and ultimately traction retinal detachment via the final common pathway (Fig. 1). Thus, the similarities of trauma and proliferative vitreoretinopathy to proliferative diabetic retinopathy are apparent. This review does not focus on the microvasculopathy of diabetic retinopathy, other than as the underlying disease process and the instigator of the final common pathway. Rather, the emphasis is on wound healing and subsequent traction retinal detachment seen in diabetic retinopathy.

The current success in treating traction retinal detachment associated with proliferative diabetic retinopathy by vitrectomy and related techniques is eloquent testimony to the contributions of the innovative clinicians and vitreous surgeons who have pioneered these remarkable advances over the past two decades. Knowledge of the pathoanatomy of the disease gained from vitreous surgery has been key to understanding this process, since there is no good animal model of this condition. The Diabetic Retinopathy Vitrectomy Study emphasized the indications for vitrectomy for traction retinal detachment and the timing for vitrectomy for vitreous hemorrhage in the diabetic eye.

The pathogenesis of traction detachment in diabetic retinopathy involves the following three major interacting mechanisms: alteration of the blood-retinal barrier, neovascularization, and vitreous contraction (Fig. 1). In the advanced stage of diabetic retinopathy, there is continued vascular leakage and inflammation that lead to cellular proliferation and the formation of new vessels that originate within the

retina and extend to the vitreoretinal interface. Vaso-occlusive processes, with resulting inner retinal hypoxia, have a key role in this process of neovascularization.[71] In normal retina, there is a balance between those factors that promote angiogenesis and those that inhibit it.[72-74] Tissue hypoxia upsets this delicate balance, and results in neovascularization. In recent years, several factors that stimulate or inhibit the proliferation of vessels in the retina have been described. A better understanding of the cellular and molecular biologic characteristics of neovascularization will aid in the design of pharmacologic agents to inhibit the stimulants of this process in the future.

Once the new vessels begin to form a strong vitreoretinal adhesion along the vitreoretinal interface, another process, vitreous separation, induced in part by shrinkage of the vitreous body, begins to have an important role in the pathogenesis of this disease.[75,76] Contraction of the vitreous gel, in the form of a partial posterior vitreous detachment, occurs more commonly and at an earlier age in diabetics than in nondiabetics,[77] and it has been observed clinically that partial vitreous detachment further stimulates proliferation of the neovascular tissue. New vessels grow along the detached posterior vitreous surface, which serves as a scaffold. Leakage from abnormal vessels initiates the inflammatory response, consisting of serum-derived cytokines, as well as circulating inflammatory cells. This combination of breakdown of the blood-retinal barrier in addition to the abnormal vitreous leads to migration and proliferation of cells as a key component of the final common pathway that results ultimately in traction detachment.

The cells in the fibrovascular membrane then contract more, thereby increasing the vitreous detachment, which allows more new cells to grow in the gap between the retina and vitreous.[78] After partially separating from the retina, the vitreous typically develops a funnel-shaped configuration that extends between the vitreous base anteriorly and areas of fibrovascular proliferation posteriorly. The areas of vitreous attachments, anteriorly at the vitreous base, and posteriorly at the optic nerve and along the major retinal vessels, determine the form of traction retinal detachment seen typically in diabetic retinopathy. The so-called wolf-jaw configuration of vitreoretinal adherence is explained on the basis of these areas of firm adherence in this pathoanatomy.

Continued shrinkage of the cortical vitreous exerts traction on the thin-walled new vessels, which may hemorrhage into the subhyaloid space, the vitreous gel, or both. The vessels are fragile and bleed easily, and the resulting hemorrhage accelerates the inflammatory response and further shrinkage of the vitreous gel, thus contributing to a vicious circle. Further vitreous traction on areas of vitreoretinal adhesion eventually results in traction retinal detachment.

The role of the posterior vitreous in the pathogenesis of traction detachment in proliferative diabetic retinopathy has been verified clinically. As already noted, the presence of a partial vitreous detachment with continued vitreous traction is a poor prognostic sign.[79] However, if vitreous detachment is complete, there is often remission of the proliferative diabetic retinopathy, with regression of new vessels and thinning of epiretinal membranes.[75] Furthermore, in eyes in which complete vitreous detachment occurs before development of neovascularization, traction retinal detachment is not seen.[77] Thus, induction of a complete vitreous detachment before new vessels start to grow may be a potential therapeutic intervention for the prevention of traction retinal detachment in diabetic retinopathy.

Before the advent of pars plana vitrectomy in the early 1970s, traction detachment of the retina, as a complication of proliferative diabetic retinopathy, was managed by scleral buckling and, in some cases, scleral resection procedures.[80] New technology in the form of automated vitrectomy via a pars plana approach, pioneered by Machemer and associates,[81-83] now provides a direct solution to the problem of vitreous traction in this condition. In the early 1970s, controversy centered on the use of vitrectomy to prevent the extension of an extramacular traction retinal detachment into the macula. Charles[84] demonstrated that diabetic traction retinal detachment of the macula could be successfully operated on by vitrectomy to relieve the traction, with resultant recovery of central vision in certain cases. Loss of central vision caused by traction detachment of the macula in diabetes is as urgent an indication for vitreous surgery as it is with rhegmatogenous retinal detachment that threatens the macula.

Initial observations after the introduction of pars plana vitrectomy indicated that complete removal of the cortical vitreous usually arrested preretinal fibrovascular growth. However, epiretinal fibrovascular tissue not removed by vitrectomy often contracted further, which resulted in continued tangential traction on the

adjacent retina.[85] On the basis of these observations, the surgical objectives in the treatment of complications of diabetic retinopathy have evolved to include the following: (1) removal of opacities that impair vision, (2) removal of the vitreous scaffold (on which abnormal fibrovascular tissue grows) to arrest progression of the neovascularization process, and (3) the removal or segmentation of all preretinal (elevated) and epiretinal (flat) fibrovascular tissue to relieve continued tangential retinal traction[78,85,86] (Fig. 12).

Visual and anatomic results after pars plana vitrectomy have been stable. One series[87] showed that about 80% of the eyes that had 20/200 or better visual acuity preoperatively continued to have equally good or better visual acuity at the five-year examination, and about half of these continued to have visual acuities at similar levels at the ten-year follow-up examination (Fig. 13). Traction that produces neovascular proliferation did not redevelop in any of the eyes after vitrectomy, once the objectives of the surgery were successfully achieved. Most vitrectomy complications, such as retinal detachment, neovascular glaucoma, and vitreous hemorrhage, occurred within the first postoperative six months. The clinical observation that there is no recurrence of neovascularization after initially successful vitrectomy emphasizes the importance of the vitreoretinal relationship in the pathogenesis of traction retinal detachment in diabetes. Once the posterior vitreous surface is removed by vitrectomy, new vessels lose the scaffold on which they grow, and the disease process is altered most profoundly. Most remarkable is that the seemingly inexorable progression of proliferative diabetic retinopathy is fundamentally altered after vitrectomy in some patients, so that retinopathy progresses no further.

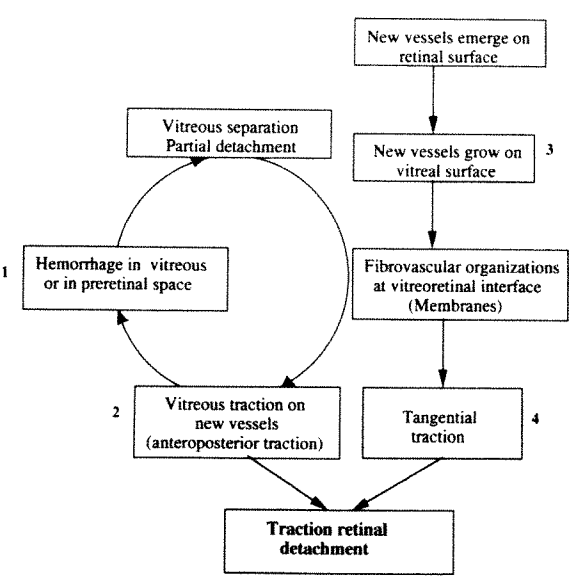


Fig. 12 (Ryan). Flow chart explaining the pathogenesis of traction retinal detachment in proliferative diabetic retinopathy. Numbers in the diagram indicate steps at which goals of vitreous surgery are aimed: (1) remove visually obstructive opacities; (2) remove anteroposterior traction of vitreous gel; (3) remove vitreous scaffold necessary for neovascular growth; and (4) remove tangential traction of membranes.

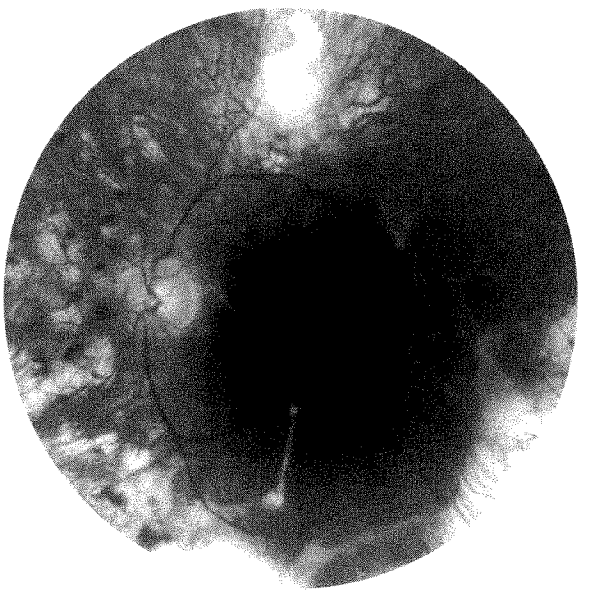


Fig. 13 (Ryan). Fundus photograph of the left eye of a patient 18 months after pars plana lensectomy, vitrectomy, membrane stripping, SF_6 gas injection, cryotherapy, and scleral buckle. Preoperative visual acuity was 20/400, and the eye had extensive traction detachment from proliferative diabetic retinopathy. Postoperative visual acuity improved to 20/50, the retina remained attached, and retinal neovascularization as well as rubeosis iridis showed involution. For the last 12 years postoperatively, the condition of the retina has remained stable.

Although our surgical objectives are unchanged, vitreous surgery techniques and instrumentation have steadily evolved; membrane delamination,[78,86] membrane segmentation,[86,88] and en bloc excision[89,90] techniques have each been recommended for the removal of preretinal and epiretinal membranes. Controversy about the efficacy of treatment provided the impetus for the creation of several na-

tional clinical trials. Such large pilot studies helped define the indications for vitrectomy in diabetic retinopathy, as well as the prognostic factors that indicate a successful surgical outcome.[85,86,91-97] Early studies indicated that patients with traction retinal detachment of the macula had a much poorer chance for improved vision.[85,92-95] Prognostic factors noted to be associated with an increased likelihood of ambulatory vision included the following: (1) preoperative visual acuity of 5/200 or better, (2) absence of iris neovascularization, (3) absence of preoperative vitreous hemorrhage, (4) prior panretinal photocoagulation, (5) absence of an iatrogenic retinal break, (6) absence of preoperative severe retinal neovascularization,[80,87,92-100] and (7) absence of lensectomy.

The most important indications for vitrectomy in diabetic retinopathy have evolved to include the following: (1) nonclearing vitreous hemorrhage of long-standing duration, (2) traction retinal detachment involving the macula, and (3) combined traction-rhegmatogenous retinal detachment.[48,79,80,82,101] The surgical results for these indications improved as advances were made in instrumentation and techniques, and visual improvement rates varied from 53% to 80%.[74,80,82,85,101]

A randomized prospective clinical trial was initiated to determine the efficacy of early vitrectomy in diabetic retinopathy. The Diabetic Retinopathy Vitrectomy Study,[102-106] a multicenter randomized prospective clinical trial supported by the National Eye Institute, was designed to evaluate the benefits of performing early pars plana vitrectomy in eyes with severe proliferative diabetic retinopathy. When the study was initially designed, vitrectomy was usually reserved for eyes with severe vitreous hemorrhage of at least one year's duration, or for eyes with traction retinal detachment involving the center of the macula.

The study of the natural course of the disease, the first report of the Diabetic Retinopathy Vitrectomy Study,[102] indicated that in those patients with severe proliferative diabetic retinopathy, decreases in visual acuity were more common during the first year of follow-up than during the second year. Decreases in visual acuity were also related to initial baseline visual acuity and to severity of retinopathy. After two years, visual acuity level was less than 5/200 in 45% of eyes that had more than 4 disk diameters of new vessels at baseline and a visual acuity of 10/30 to 10/50; 23% of eyes with extramacular traction retinal detachment had visual acuity of less than 5/200 at the two-year visit. Interestingly, Charles and Flinn[107] found only a 21% rate of progression of extramacular traction retinal detachment extending into the macula after a two-year period. Their study suggested that, in cases of extramacular traction detachment, immediate intervention at the time of separation of the macula, rather than a prophylactic procedure, was the most effective therapy.

The benefits of early vitrectomy in severe proliferative diabetic retinopathy were described in the second, third, and fifth reports from the Diabetic Retinopathy Vitrectomy Study Research Group.[103,104,106] Early vitrectomy with conservative management in eyes with recent vitreous hemorrhage and visual acuity reduced to 5/200 or less for at least one month was described in the second and fifth reports.[103,106] Vitrectomy was performed either shortly after randomization or was deferred until one year after the onset of hemorrhage (unless retinal detachment of the center of the macula occurred before that date). The results of this study clearly indicated that early vitrectomy was beneficial and enhanced the chance for recovery of good vision. Patients with type I diabetes had a clear benefit from early vitrectomy, since 36% of these patients obtained a visual acuity of better than or equal to 10/20 at two years; this was compared with only 12% of similar patients who were treated conservatively. Further analysis of the four-year follow-up study[106] disclosed that patients with type I diabetes of less than 20 years' duration benefited the most from early vitrectomy. The advantage of early vitrectomy was not found in patients with type II diabetes who were older and who tended to have less severe retinopathy. Interestingly, visual results in patients on whom vitrectomy was performed appeared to stabilize after only six months, which is in good agreement with other long-term clinical studies.[87,98-100]

The third report from the Diabetic Retinopathy Vitrectomy Study[104] compared early vitrectomy with conventional management in eyes with extensive active neovascular proliferation and with visual acuity of 10/200 or better. The four-year follow-up results of this study showed that the percentage of eyes with a visual acuity of 10/20 or better was 44% in the early vitrectomy group and 28% in the conventional treatment group. This finding demonstrated that the advantage of early vitrectomy was also particularly marked in patients with type I diabetes. These results strongly suggest-

ed that the more extensive the new vessels, and the worse the outlook for improvement with additional photocoagulation, the more seriously early vitrectomy should be considered.

The treatment of diabetic traction retinal detachment has continued to evolve with additional modifications in surgical approach. Prophylactic scleral buckling and cryopexy are no longer routinely performed, since several large studies have shown that these procedures are of no benefit in preventing retinal detachment.[87,98-100] Another advance in treatment, however, has been the realization that lensectomy during vitrectomy for complications of diabetic retinopathy is clearly not beneficial. The increased incidence of iris rubeosis and neovascular glaucoma after lensectomy has been well documented.[108,109] The standard of care now includes preservation of the lens, whenever possible, in such surgery. The introduction of intraocular argon laser photocoagulation represents still another major advance in our surgical treatment of diabetic retinopathy.[110] Intraoperative endophotocoagulation has reduced the incidence of recurrent vitreous hemorrhage after vitrectomy for proliferative diabetic retinopathy.[111] It is now standard practice to apply scatter endophotocoagulation at the time of vitrectomy for complications of this disease.

New indications for early vitrectomy in proliferative diabetic retinopathy have been advocated.[112] One such indication is premacular subhyaloid hemorrhage in eyes with active proliferative retinopathy. Hemorrhage into the premacular subhyaloid space may accelerate the contraction of fibrovascular membranes, which can cause bleeding and retinal traction. Vitreous surgery may prevent the pigment epithelial deterioration that is seen commonly after resolution of the hemorrhage, and may preclude foveal ectopia from epiretinal membrane contracture.[113,114] Similarly, early vitrectomy has been advocated in eyes with a partial posterior vitreous detachment and retinal traction from proliferative tissue along the retinal arcades and optic disk.[115] Another contemporary indication for early vitrectomy is progressive fulminant neovascular proliferation uncontrolled by extensive panretinal photocoagulation.[112] These patients typically have rapidly progressive diabetic retinopathy, despite a short history of diabetes mellitus; their diabetes is usually poorly controlled with medical treatment, with renal insufficiency and loss of antithrombin III in the urine.

New challenges in the clinical care of patients with complications of proliferative diabetic retinopathy remain to be addressed. In particular, the surgical management of progressive retrolental fibrovascular proliferation after vitrectomy remains a complex issue.[116,117] The use of silicone oil may be beneficial in these cases, but more studies are certainly needed.[116]

What frontiers lie on the horizon in the care of patients with neovascular proliferation in diabetic retinopathy? Clearly, there has been tremendous growth of our understanding of the cytologic characteristics of neovascularization,[71-74,118] and practical application of this information, obtained through laboratory science, will ultimately help us in the care of diabetic patients. While diabetic retinopathy is the most important vascular disease affecting the eye, the diabetic traction detachments are based on the inflammatory and wound-healing response, the components of the final common pathway. The knowledge obtained from laboratory research, in conjunction with future clinical research, regarding both the vascular and wound-healing responses, will continue to improve the care of patients with the traction retinal detachment of proliferative diabetic retinopathy.

Discussion

The goals of this review were, first, to describe a final common pathway for traction retinal detachments, and, second, to stress the close reciprocal relationship of progress in basic and clinical research to progress in clinical practice.

The response of the eye to injury, be it traumatic, metabolic, toxic, inflammatory, or degenerative, is limited. Accordingly, there are important final common pathways to a variety of different ocular diseases. The identification of such common pathways aids in the design of rational treatment.

I emphasized that traction retinal detachment is the end point of the final common pathway in three apparently different diseases: penetrating ocular trauma, proliferative vitreoretinopathy, and proliferative diabetic retinopathy. Each of these three diseases shares common features; an inflammatory response with breakdown of the blood-retinal barrier, combined with abnormal vitreous, results in migration and proliferation of cells. As part of the wound-healing response, these cells contract and lay down extracellular matrix, including

collagen. When they reach a critical mass such that their force of contraction exceeds the force of retinal attachment, traction retinal detachment occurs (Fig. 1). These three disease processes have many differences, such as the inciting or triggering events, time course, aspects of the cellular response, and primary anatomic location of involvement. The commonality shared by these three diseases, however, outweighs the heterogeneity when it comes to the final common pathway that leads to traction detachment.

The abnormal biologic characteristics of these three conditions are also similar in many respects. After penetrating ocular injury with intraocular bleeding, it is apparent there is a wound-healing response that is similar to that elsewhere in the body. Inflammation initiates the final common pathway (Fig. 1), characterized by an initial polymorphonuclear response that, in turn, elicits the critically important process of recruitment of macrophages from the systemic circulation and nearby tissues. These macrophages release numerous factors that recruit additional macrophages that amplify the inflammation and, as with wound healing elsewhere in the body, recruit fibroblasts and myofibroblasts, which form membranes. The myofibroblasts have a pivotal role in generating tractional forces. We have measured the contraction force generated by these membranes, and have shown that they do respond to various pharmacologic agents.

The rationale of our current approach to the treatment of traction detachment is based on our understanding of the pathoanatomic and pathobiologic aspects of each condition. Vitrectomy clearly provides an opportunity to relieve the traction and to restore anatomic integrity. Additionally, vitrectomy has an important role in removing the stimulus to further inflammation, and thus attenuates the wound-healing response.

Several important questions remain to be answered. Breakdown of the blood-retinal barrier occurs in trauma, proliferative vitreoretinopathy, and in proliferative diabetic retinopathy, and allows serum-derived growth factors and cytokines to leak across the impaired blood-retinal barrier and initiate the inflammation that drives the proliferative process. Knowledge of the blood-retinal barrier and how it is modulated could provide a major opportunity for medical intervention in these and other disease processes.

In addition to macrophages, the retinal pigment epithelium seems to be a principal cellular source of the regulatory factors that direct the overall course of proliferative vitreoretinopathy. We need to understand which cytokines and growth factors are produced by the retinal pigment epithelial cells, and how their expression is modulated, to control the process medically. The delivery of drugs and biologic response modifiers to the retina is a potentially fertile area of research that has received little attention.

There have been considerable advances in intraocular surgery since the 1970s, when Machemer popularized vitrectomy; patients with traction detachments are no longer treated with bedrest and consigned to blindness. Our ability to prevent or arrest the blinding progression of intraocular proliferation is one of the great success stories of medicine, and is the result of clinical observation, innovative technology, extensive research on animal models, and generous support of basic research and clinical trials by the National Eye Institute. The National Eye Institute has been a critical factor in this success story. Through its basic research support programs and national trials, such as the Diabetic Retinopathy Study, the Diabetic Retinopathy Vitrectomy Study and the current Silicone Study, new treatment regimens have been defined and have received consensus support.

Future Directions for Research and Treatment of Traction Detachments

The sight-saving successes of vitreoretinal surgery in the past decade, although remarkable, are only a small indication of the progress we can expect to see in the next 20 years as the impact of molecular medicine reaches clinical practice. Virtually all clinical research on retinal detachment, and subsequently our clinical practice, has focused on the final step, namely the traction retinal detachment. For instance, the Diabetic Retinopathy Vitrectomy Study, the Silicone Oil Study, and numerous other studies are all concerned with intervention in this final step. Only in proliferative vitreoretinopathy has there been an attempt to intervene at an earlier step, namely the proliferation and migration of contractile cells. Various chemotherapeutic agents, such as 5-fluorouracil, daunorubicin, colchicine, and corticosteroids, have been used in an attempt to interrupt the final common pathway. Retinal toxicity and the inherent problems of drug delivery have limited the feasibility of drug therapy. Recently, much progress has been made in the delivery and use of chemotherapeutic agents in glaucoma, and

similar applications in vitreoretinal surgery may soon be found.

This progress foreshadows a new technological era of subretinal surgery and adds urgency to our need for methods of photoreceptor and retinal pigment epithelium rescue through transplantation or application of appropriate neurotrophic factors. Photoreceptor function is gradually lost in detached retinas, and is restored by reattachment as the lost outer segments are renewed and come into contact with the retinal pigment epithelium. We must understand this process better to prevent the functional loss or to facilitate the renewal.

The challenge to our basic-science research colleagues during the next decade is to identify and understand the effects of the many extracellular factors, not in isolation, but in relation to a long chain of wound-healing events that are intertwined, interdependent, complex, and profoundly influenced by the immediate environmental milieu. However, such an awesome challenge promises equally awesome rewards. The potential benefit of using selected inhibitory extracellular factors to interfere with the proliferation and migration of retinal cells or with the breakdown of the blood-ocular barrier, and in effect abort this entire process, is enormous.

Posterior vitreous detachment occurs under certain conditions and protects the diabetic eye from vitreous neovascularization. When we understand the biologic process of the detachment, we may be able to induce it with appropriate application of various extracellular factors. This accomplishment should be immensely helpful to our diabetic patients, and is an important goal for future research.

Lest one think that these potential therapeutic interventions are too futuristic or outlandish, one need only think of the meager treatment we had to offer our patients with traction retinal detachments before the development of vitrectomy instrumentation, endolaser, gas and silicone tamponade, and ocular chemotherapeutic agents. No doubt our current management will be similarly outdated 20 years from now. During the next two decades we will see an explosion of information from the various fields of research. It will be our responsibility in the ophthalmic community to assess and synthesize this information as it applies to our patients. Moreover, when vexing and important questions remain, we, as clinical practitioners, must guide the direction of research. Such guidance may range from sharing our clinical experience in meetings or in publications, to demanding a well-run, prospective, multicenter study. With every new development comes a new challenge: our challenge as patient advocates is to be active participants in the design, progress, synthesis, and application of clinical, animal, and laboratory research.

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OPHTHALMIC MINIATURE

The eyes were traditionally held to be the "windows of the soul" and capable of expressing the feelings of a person. Certain people, kings and commoners alike, were thought to have the Evil Eye and could bring disaster upon those they looked at. The Evil Eye was a popular superstition in Europe for centuries and still lingers on in Italy and Sicily. In England it was thought that only the first glance of the day was malevolent, and there is an account of man in Yorkshire said to be cursed with this characteristic who made sure that his first glance each morning should be directed on a pear tree outside his window, so dissipating its evil influence. The tree, it is said, eventually withered and died. Those possessed of the Evil Eye had no control over its action, and in some cases were even unaware they had it. The Emperor Napoleon III of France knew himself to have the Evil Eye and wore a talisman on his watch-chain to counteract its effect.

John Camp, *Magic, Myth and Medicine*
London, Priory Press, 1973, pp. 127–128

Photoreceptor Outer Segments in the Aqueous Humor of Patients With Atopic Dermatitis and Retinal Detachment

Nobuhiko Matsuo, M.D., Toshihiko Matsuo, M.D., Fumio Shiraga, M.D., Akira Hosoda, B.S., Youko Kawanishi, M.D., Sei Watanabe, M.D., and Hiroshi Ohtsuki, M.D.

We examined the aqueous humor by electron microscopy of four patients with atopic dermatitis and retinal detachment. All the patients had a moderate number of cells in the aqueous humor. Cataract impaired fundus visualization except for one patient with aphakia. A flat retinal detachment involved a wide area detected by echography. The intraocular pressure in the eyes with retinal detachment demonstrated a marked diurnal fluctuation compared with that of the fellow eye.

The aqueous cells consisted predominantly of photoreceptor outer segments. This finding does not support the theory that aqueous cells in atopic dermatitis are of inflammatory origin. Photoreceptor outer segments in aqueous humor are indicative of rhegmatogenous retinal detachment in patients with atopic dermatitis.

OCULAR COMPLICATIONS of atopic dermatitis include blepharitis, keratoconjunctivitis, keratoconus, iritis, cataract, and retinal detachment.[1,2] Atopic dermatitis usually begins in infancy or at preschool age but some patients develop the disease after puberty.

Retinal detachment in patients with atopic dermatitis is usually the result of an oral dialysis or tears of the nonpigmented epithelium of the pars plana or plicata of the ciliary body.[3-10] Cataract often impairs visualization of the fundus and delays the diagnosis of retinal detachment.

Rhegmatogenous retinal detachment with oral dialysis or tears of the nonpigmented epithelium of the ciliary body is sometimes associated with high intraocular pressure and the occurrence of cells in the anterior chamber.[11,12] After successful reattachment of the retina, the cells in the aqueous humor usually disappear and the intraocular pressure returns to normal. The condition is called Schwartz syndrome.[11,12] The cells in the aqueous humor consist predominantly of photoreceptor outer segments and not inflammatory cells.[13,14] We examined aqueous humor cells by electron microscopy in four patients with atopic dermatitis and retinal detachment, and demonstrated these cells to be predominantly photoreceptor outer segments.

Patients and Methods

We studied ten consecutive patients (12 eyes) with atopic dermatitis and retinal detachment between June 1989 and May 1992. Atopic dermatitis developed in the preschool years in each patient and usually became exacerbated after adolescence (Table). Anterior and posterior subcapsular cataract was found in all the patients except for one, who had previously undergone extracapsular cataract extraction. The area and height of retinal detachment were determined with echography, as the cataract prevented the fundus from being clearly visualized in most of the patients. Pars plana lensectomy (omitted in the aphakic patient) and vitrectomy combined with encircling, internal drainage of the subretinal fluid through an intentional retinotomy, fluid-gas exchange, endophotocoagulation, and gas tamponade with sulfur hexafluoride were performed in all the eyes except for the aphakic left eye of the patient in Case 1 and the right eyes of the

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From the Department of Ophthalmology, Okayama University Medical School, Okayama City, Japan.

Reprint requests to Toshihiko Matsuo, M.D., Department of Ophthalmology, Okayama University Medical School, 2-5-1 Shikata-cho, Okayama City, Okayama 700, Japan.

TABLE
SUMMARY OF FOUR PATIENTS WITH ATOPIC DERMATITIS AND RETINAL DETACHMENT

CASE NO., AGE (YRS), GENDER	EYE	RETINAL DETACHMENT		MACULAR INVOLVEMENT	TEAR(S)		BEST-CORRECTED VISUAL ACUITY	
		HEIGHT	AREA (QUADRANT)		LOCATION	EXTENT (O'CLOCK MERIDIAN)	PREOPERATIVE	POSTOPERATIVE
1, 20, M	L.E.	Flat	3	No	Ora serrata	1-3 and 4:30-6:30	20/15	20/20
	R.E.	Flat	2	No	Ora serrata	1-2	20/20	20/20
3, 24, F	R.E.	Flat	2	No	Pars plana	12-4	20/100	20/30
4, 17, M	L.E.	Flat	1	No	Pars plana	4-5	20/50	20/20
9, 23, M	R.E.	Flat	2	No	Ora serrata	9-10	20/100	20/20

patients in Cases 1 and 7, who were treated only with scleral buckling. The retina was reattached successfully in all the patients.

Anterior chamber paracentesis was performed and aqueous humor was obtained from seven (right eye in Cases 1, 3 through 6, and 9; and left eye in Case 7) of the ten eyes with cells in the aqueous humor. Paracentesis was not performed in the remaining three eyes with aqueous cells because the consent to the procedure was not obtained. The aqueous humor from four eyes (right eye in Cases 1, 3, 4, and 9) was processed successfully for electron microscopy. The cells in these eyes consisted predominantly of photoreceptor outer segments (Figs. 1 through 3). There were also macrophages that phagocytosed photoreceptor outer segments (Fig. 1). No inflammatory cells such as lymphocytes or polymorphonuclear leukocytes were observed in the aqueous humor of any patient.

The pellet of aqueous cells obtained from the other three eyes of the three patients was too small to permit sectioning. There were no complications caused by the anterior chamber paracentesis in any patient.

Case Reports

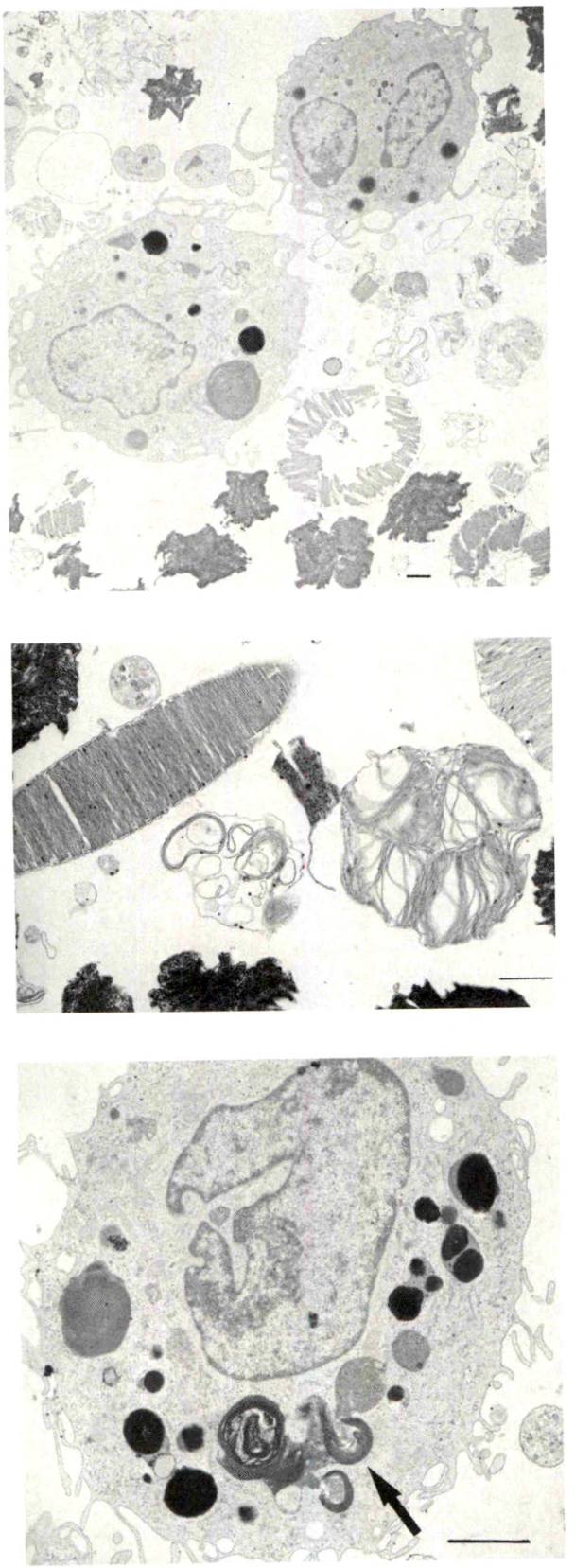
Case 1

A 20-year-old man had had atopic dermatitis and bronchial asthma since infancy. He had undergone scleral buckling for retinal detachment with midperipheral tears in both eyes five years earlier and extracapsular cataract extraction in each eye four years earlier. He noticed a defect in the upper half visual field of the left eye and was referred to our hospital. On initial examination, the best-corrected visual acuity was R.E.: 20/10 and L.E.: 20/15. No cells were observed in the anterior chamber or vitreous, and the posterior capsule was intact in the right eye. A moderate number of aqueous cells, pigment clumps in the anterior vitreous, and an intact posterior capsule were observed in the left eye. The intraocular pressure was 14 mm Hg in the right eye and 15 mm Hg in the left eye. He had flat detachment involving the lower half and left upper quadrant of the retina with oral dialysis that extended from the 1 to 3 o'clock meridians and the 4:30 to 6:30 o'clock meridians in the left eye. He underwent pars plana vitrectomy, and gas-fluid exchange with aspiration of subretinal fluid through an intentional retinotomy, followed by endophotocoagulation. The retina was reattached and the visual acuity in the left eye returned to 20/20.

Six months later, he developed flat detachment in the right eye that extended from the upper midperiphery to the lower half of the retina with oral dialysis from the 1 to 2 o'clock meridians. He had a moderate number of cells in the aqueous humor in the right eye, but no cells in the aqueous humor in the left eye. The intraocular pressure was 11 mm Hg in both eyes. There was diurnal fluctuation of the intraocular pressure (11 to 18 mm Hg) in the right eye, with higher values in the evening, whereas the intraocular pressure in the left eye remained relatively unchanged. The retina was reattached by scleral buckling with gas tamponade. The final visual acuity in the right eye was 20/20.

Case 3

A 24-year-old woman with atopic dermatitis since 3 years of age began to have exacerbation of the dermatitis in the recent 18 months. She noted blurred vision in the right eye. On the initial visit, the best-corrected visual acuity was R.E.: 20/100 and L.E.: 20/15. She had a moder-



ate number of cells in the aqueous humor, and anterior and posterior subcapsular cataract in the right eye. The right fundus was invisible and a flat temporal retinal detachment was observed by echography. The left eye was normal. The intraocular pressure was 13 mm Hg in both eyes. The tonographic c value was 0.07 in the right eye and 0.15 in the left eye. The intraocular pressure in the right eye showed diurnal fluctuation that ranged from 9 to 17 mm Hg, whereas the left eye had no remarkable change. She underwent pars plana lensectomy, vitrectomy combined with scleral buckling, cryocautery, gas-fluid exchange, and endophotocoagulation. Intraoperatively, a tear of the nonpigmented epithelium of the pars plana was found, which extended from the 12 to 4 o'clock meridians. The visual acuity in the right eye became 20/30 after the retinal reattachment.

Case 4

A 17-year-old boy with atopic dermatitis since 3 years of age began to notice floaters in the left eye for three months before initial examination. The best-corrected visual acuity was R.E.: 20/15 and L.E.: 20/50. The right eye was normal. The left eye had a moderate number of cells in the aqueous humor, and anterior and posterior subcapsular cataract that hindered clear visualization of the fundus. Echography demonstrated flat retinal detachment that extended from the superior to the temporal quadrants and spared the macula. The intraocular pressure was 16 mm Hg in the right eye and 20 mm Hg in the left eye. The left eye showed diurnal fluctuation of the intraocular pressure that ranged from 10 to 27 mm Hg, with higher values in the evening. The right eye had no such fluctuation. The tonographic c value in the right eye was 0.21, whereas the value in the left eye was 0.07 on one occasion and 0.22 on another occasion. He underwent pars plana lensectomy, vitrectomy, gas-fluid exchange, and endophotocoagulation combined with encircling. A tear of the nonpigmented epithelium of the pars plana that extended from the 4 to 5 o'clock meridians was observed intraoperatively. The

Fig. 1 (Matsuo and associates). Case 1. Top and middle, Aqueous cells in the right eye consist of photoreceptor outer segments and macrophages. Bottom, A macrophage phagocytoses photoreceptor outer segments (arrow) (uranyl acetate and lead citrate; bar = 1 μm).

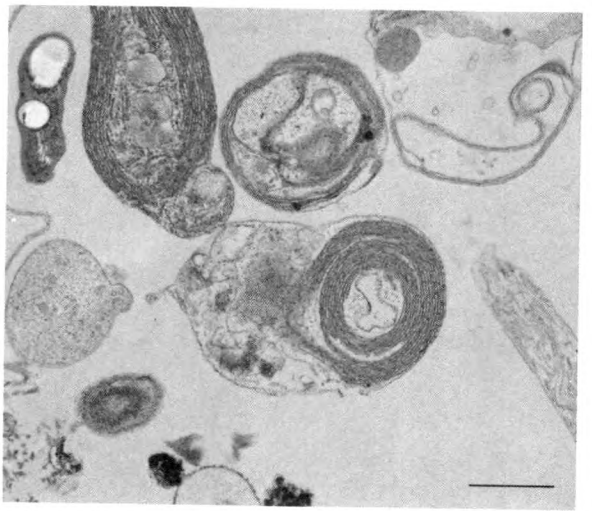


Fig. 2 (Matsuo and associates). Case 3. Photoreceptor outer segments in the aqueous humor (uranyl acetate and lead citrate; bar = 1 μm).

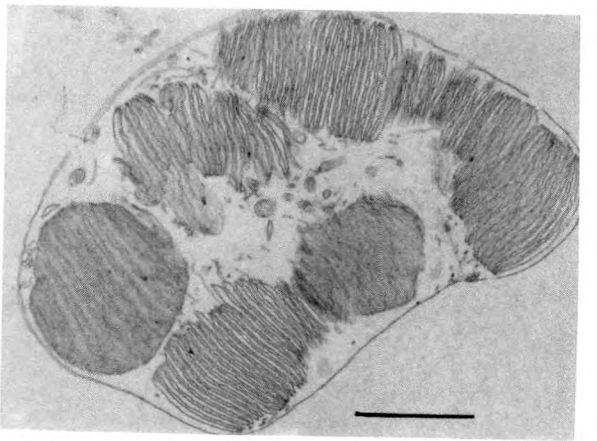


Fig. 3 (Matsuo and associates). Case 4. Photoreceptor outer segments in the aqueous humor (uranyl acetate and lead citrate; bar = 1 μm).

visual acuity in the left eye became 20/20 after the retinal reattachment.

Case 9

A 23-year-old man had developed atopic dermatitis in infancy and experienced exacerbation for two years before initial examination. He noticed floaters and blurring in the right eye. On the initial examination, the best-corrected visual acuity was R.E.: 20/100 and L.E.: 20/15. The right eye had a moderate number of cells in the aqueous humor, and anterior and posterior subcapsular cataract. Echography showed flat retinal detachment that involved the lower half, but spared the macula in the right eye. The left eye was normal. The intraocular pressure was 11 mm Hg in the right eye and 16 mm Hg in the left eye. The right eye showed marked diurnal fluctuation of the intraocular pressure that ranged from 11 to 21 mm Hg, with higher values in the evening. Tonographic c values were 0.11 in the right eye and 0.21 in the left eye. Phacoemulsification and pars plana vitrectomy combined with scleral buckling, fluid-gas exchange, and endophotocoagulation were performed in the right eye. Oral dialysis that extended from the 9 to 10 o'clock meridians was found intraoperatively. The retina was reattached and the visual acuity became 20/20 in the right eye.

Discussion

Particulate materials in the aqueous humor of patients with atopic dermatitis are usually considered inflammatory cells such as lymphocytes and polymorphonuclear leukocytes, and iritis is diagnosed in such patients. However, the aqueous structures were shown to be mainly photoreceptor outer segments in the four patients with atopic dermatitis and retinal detachment.

Each of the four patients with photoreceptor outer segments demonstrated in the aqueous humor had similar characteristics, including flat extensive retinal detachment and oral dialysis or tears of the nonpigmented epithelium of the pars plana of the ciliary body. There were also diurnal fluctuation of the intraocular pressure and no clinical signs of anterior segment inflammation, such as ciliary injection, keratic precipitates, and posterior and anterior iris synechiae. These clinical features are consistent with those described for Schwartz syndrome.[13-15] Therefore, the presence of cells in the aqueous humor of patients with atopic dermatitis suggests the possibility of a retinal detachment with tears located at or near the ora serrata. Complicated cataract is usually present in these patients and hinders clear visualization of the fundus. Echography should be performed to exclude retinal detachment in such eyes.

The intraocular pressure was increased in only one patient (Case 4), whereas the other three patients showed a relatively normal range of the intraocular pressure. This is not consistent with the increased intraocular pressure seen in the Schwartz syndrome.[11-15] There are two possible explanations of the normal intraocular pressure in the patients with atopic dermatitis and retinal detachment. First, although

aqueous humor outflow is reduced by photoreceptor outer segments in the trabecular meshwork, the production of aqueous humor is also reduced by damage to the ciliary epithelium by the atopic inflammation. The intraocular pressure is thus not increased. Second, the number of photoreceptor outer segments is too few to impair aqueous outflow.

Processing of the cells in the aqueous humor failed in the three patients. The pellet of the cells in the aqueous humor obtained after centrifugation was not large enough to process. On the basis of our experience, the procedure worked well in the patients who had a large number of cells in the anterior chamber. When the number of cells was small, the pellet was too small and was lost during the trimming of epoxy resin after a tube tip that contained the pellet was embedded in resin. Furthermore, the procedure is complicated because the photoreceptor outer segments cannot be identified by light microscopy. It is necessary to improve the collection of aqueous cells to obtain consistent results.

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Serum Levels of Interleukin-2 Receptor in Ocular Behçet's Disease

David BenEzra, M.D., Genia Maftzir, M.Sc., Ina Kalichman, M.Sc., and Vivian Barak, Ph.D.

Serum interleukin-2 receptor levels were evaluated in 69 patients who had chronic bilateral uveitis and in 22 control subjects. Fifty-one of the 69 patients with uveitis had the ocular type of Behçet's disease and 18 had pars planitis (intermediate uveitis). The mean serum interleukin-2 receptor level was 412.6 ± 94.6 U/ml for the control group, 465.0 ± 96.6 U/ml for the patients with intermediate uveitis, and 810.9 ± 369.3 U/ml for those with ocular Behçet's disease. The serum interleukin-2 receptor levels of patients with ocular Behçet's disease were significantly different from the levels of both the control and the intermediate uveitis groups ($P < .001$). The differences in serum levels of patients with intermediate uveitis and the levels of the control subjects were not statistically significant.

Treatment of patients with ocular Behçet's disease for four to six weeks with either cyclosporine, methylprednisolone, or a combination of both, decreased the intraocular inflammation in nearly all cases. The influence of treatment on the level of serum interleukin-2 receptor, however, was variable.

Interleukin-2, a T-cell lymphokine, is a growth and activation factor for T and B cells, as well as for natural killer cells and monocytes.[1] The final effects of interleukin-2 depend on the phenotype of the target cell, the presence of specific receptors on the cell membrane, and on the presence of other stimuli.[2] Both B and T cells can express the following three types of interleukin-2 receptors on their membrane: a low-affinity binding site receptor, an intermediate-affinity binding site receptor, and a high-affinity binding site receptor. The low-affinity receptor is a 55-kd protein that apparently is unable to deliver a signal to the cell. The intermediate-affinity receptor is a 70-kd protein that is the receptor for a different part of the interleukin-2 molecule and has the ability to transduce an activation signal to the cell. The high-affinity interleukin-2 receptor is expressed by the combination receptor of both the 55-kd and 70-kd proteins.[3] The low-affinity and the high-affinity receptors are transiently up-regulated after the activation of T cells by antigens or mitogens, whereas the intermediate affinity (70-kd protein) is expressed constitutively.[4,5] After up-regulation, the level of interleukin-2 receptors on the cell membrane declines rapidly and a soluble form is shed from the membrane. The secreted (soluble) interleukin-2 receptors are glycoproteins with a molecular weight slightly lower than 55 kd, which bind specifically the interleukin-2 molecule.[6]

High serum levels of interleukin-2 receptors are believed to be associated with an activation of the immune system.[7] Increased levels have been found also in T-cell leukemias and lymphomas.[8] Furthermore, a correlation between the level of interleukin-2 receptors and arthritic symptoms in patients with Behçet's disease,[9] disease activity in rheumatoid arthritis,[10] and with graft rejection after renal allograft transplantation has been described.[11,12] Recently, an increase in interleukin-2 receptor serum levels has been detected in a few patients with Fuchs' heterochromic cyclitis and in four patients with juvenile rheumatoid arthritis and uveitis.[13]

We evaluated the serum levels of interleukin-2 receptor in patients with Behçet's disease

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From the Immuno-Ophthalmology Unit (Dr. BenEzra and Ms. Maftzir), and the Department of Oncology (Ms. Kalichman and Dr. Barak), Hadassah University Hospital, Jerusalem, Israel.

Reprint requests to David BenEzra, M.D., Immuno-Ophthalmology Unit, Department of Ophthalmology, Hadassah University Hospital, P.O. Box 12000, 91120 Jerusalem, Israel.

(ocular type) or pars planitis (intermediate uveitis), and studied the effect of treatment on these levels.

Subjects and Methods

Subjects—Sixty-nine patients with chronic uveitis of two to eight years' duration and 22 control subjects matched for age and gender were included in the study. Of the patients with uveitis, 51 had the ocular type of Behçet's disease,[14] and 18 patients had pars planitis (intermediate uveitis). All patients had chronic intraocular manifestations of the disease, with periodic intermittent sudden exacerbations of the inflammatory processes. The degree of ocular inflammation on initial examination at the clinic was arbitrarily scored as mild (grade 1), moderate (grade 2), severe (grade 3), and precarious (grade 4) according to the relative interference with the view of the fundus when examined with an indirect ophthalmoscope.[15,16] A blood sample was also taken at this visit for evaluation of the serum interleukin-2 receptor level. An attempt to correlate the degree of intraocular inflammation with the serum interleukin-2 receptor levels in patients with Behçet's disease was made. In 35 patients with ocular Behçet's disease, serum samples were obtained at the time of the first examination (before treatment) and at various intervals after initiation of medical treatment either with cyclosporine at initial dosages of 5 mg/kg of body weight/day orally, methylprednisolone at an initial dosage of 1.0 to 2.0 mg/kg of body weight/day orally, or a combination of both as described.[16] The levels of serum interleukin-2 receptors were evaluated before treatment and four to six weeks after initiation of treatment. For comparison, 22 volunteers matched for gender and age were also tested in parallel and served as control subjects. From three volunteers, sera were sampled twice (four- to six-week interval), while seven patients' sera were randomly retested in a masked manner to evaluate the accuracy of interleukin-2 receptor level measurements.

Interleukin-2 receptor assay—The blood was withdrawn from the cubital vein, transferred into sterile plastic tubes, and was incubated at room temperature (17 to 20 C) for 60 minutes. After the incubation, the tubes were centrifuged at 2,000 g for 20 minutes. The serum was transferred through a pipette into sterile vials and kept at −70 C until assayed.

Interleukin-2 receptor immunoassay kits (Cellfree, T-cell Sciences Inc., Cambridge, Massachusetts) were used throughout the study. The tests were performed in duplicate for each sample and a standard curve was prepared for each kit. The various reagents were prepared and added to the wells according to the instructions for preparation provided with each kit. In brief, the method is essentially based on the following. Polystyrene microtiter wells are coated with monoclonal antibody against interleukin-2 receptor, and reacted with sera of the unknown patient or standard interleukin-2 receptor dilutions. Unbound components are removed by washing the wells with buffered solution. After washing, horseradish peroxidase, conjugated with monoclonal anti-interleukin-2 receptor directed against a second epitope of this receptor, is added to the wells. The enzyme-conjugated anti-interleukin-2 receptor binds to the receptor captured by the first (coating) monoclonal antibody, thus completing the reaction. Unbound enzyme-conjugated anti-interleukin-2 receptor is carefully washed away before an enzyme substrate consisting of O-phenylene-diamine and 0.01% hydrogen peroxide is added to the wells. After 30-minute incubation, the enzymatic reaction is blocked and terminated by the addition of a stop solution (4N sulfuric acid). The extent of reaction in each well depends on the amount of conjugated horseradish peroxidase present. The amount of horseradish peroxidase is proportional to the level of interleukin-2 receptor trapped by the first coating monoclonal antibody. The resulting color intensity in each well is assessed by an autoreader calibrated for absorbance at 490 mm. A standard curve is prepared from four interleukin-2 receptor standards. Unknown serum values are evaluated in relation to the standard curve obtained for each batch of tests. The values are indicated in units per milliliter. A value of 1,000 U/ml has been arbitrarily determined as the level of interleukin-2 receptor obtained from a supernatant of human lymphocyte culture stimulated with phytohemagglutinin.

Statistical analysis—The among-group differences of serum interleukin-2 receptor levels were examined by using one-way analysis of variance. The significance of differences between means of any two groups was determined by using the modified Tukey method for multi-

ple comparisons with an α value of 0.05.[17] Significance in the F ratio test is indicated when a P value less than .001 is achieved.

Results

Sera from three normal volunteers obtained at intervals of four to six weeks demonstrated a slight variability in their interleukin-2 receptor levels, with a maximum of 66 units difference between the two tests. These values were smaller than the standard deviation of the whole control group. The masked evaluation of seven patients' serum samples randomly tested twice yielded interleukin-2 receptor levels with a maximum deviation of 65 units. The initial serum levels were observed for individual patients with ocular Behçet's disease, patients with intermediate uveitis, and the normal control subjects (Fig. 1). A wide range of serum interleukin-2 receptor levels was observed in all three groups. The levels in the control subjects ranged between 215.0 and 573.0 U/ml (mean, 412.6 ± 94.6 U/ml). The levels of the patients with intermediate uveitis ranged from 233.0 to 624.0 U/ml (mean, 465.0 ± 96.6 U/ml), whereas in the sera of patients with ocular Behçet's disease, the minimum level recorded was 310.0 U/ml and the maximum level recorded was 2,040.0 U/ml (mean, 810.9 ± 369.3 U/ml). Using one-way statistical analysis of variance followed by the Tukey method for multiple comparisons (α = 0.05), the mean serum interleukin-2 receptor level of patients with intermediate uveitis was not statistically different from the level observed in sera from normal volunteers. However, the mean level of patients with ocular Behçet's disease was significantly higher than the values obtained for the normal control subjects and the patients with intermediate uveitis ($P < .001$). Only two of 51 patients with ocular Behçet's disease had an initial serum interleukin-2 receptor level lower than the normal mean level, whereas 40 patients had levels higher than the normal mean + 1 standard deviation. Furthermore, 34 of these patients had an interleukin-2 receptor level higher than the normal mean + 2 standard deviations (Fig. 1).

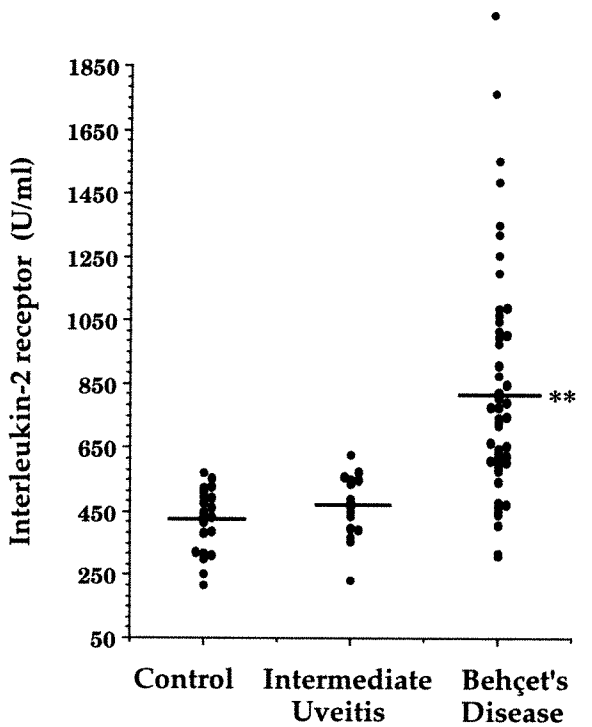


Fig. 1 (BenEzra and associates). Interleukin-2 receptor levels in sera of patients with intermediate uveitis, ocular Behçet's disease, and in normal volunteers (control subjects). Each dot represents the level detected at time of initial examination at the clinic. The bars represent the mean interleukin-2 receptor level for each group.

On initial examination at the clinic, more patients with ocular Behçet's disease and a low degree (grade 1) of intraocular inflammation had a serum interleukin-2 receptor level lower than 500 U/ml, whereas nine of 12 patients (75%) with levels higher than 1,000 U/ml had precarious (grade 4) intraocular manifestations (Fig. 2). Nonetheless, no absolute correlation between the serum interleukin-2 receptor level and the degree of intraocular inflammation was found. At initial examination, some patients with interleukin-2 receptor levels lower than 500 U/ml had severe (grade 3) or precarious (grade 4) intraocular manifestations, while three of 12 patients (25%) with serum interleukin-2 receptor levels higher than 1,000 U/ml had a moderate (grade 2) intraocular inflammation (Fig. 2).

After systemic treatment with cyclosporine, methylprednisolone, or a combination of both for four to six weeks, only a slight and variable effect on the level of serum interleukin-2 receptor was observed when the pretreatment levels were 800 U/ml or less (Fig. 3). However, 11 of the 12 patients with pretreatment serum interleukin-2 receptor levels higher than 800 U/ml

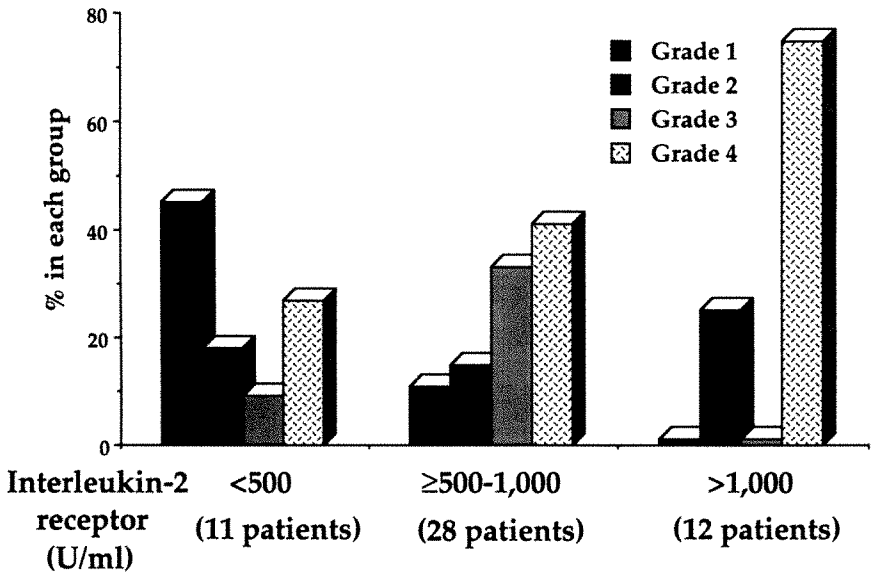


Fig. 2 (BenEzra and associates). Correlation between serum interleukin-2 receptor level and the degree of intraocular inflammation. The height of the columns illustrates the percentage of patients with the indicated grade of intraocular inflammation for three different ranges of serum interleukin-2 receptor levels at initial examination.

had a lower serum level after treatment. Clinically, ten of these 11 patients had a favorable therapeutic response with a good control of the intraocular inflammation. However, the ocular condition steadily worsened in one patient despite the recorded decrease of serum interleukin-2 receptor level after treatment. In one of the 12 patients with pretreatment serum interleukin-2 receptor levels higher than 800 U/ml, the level of serum interleukin-2 receptor increased after treatment (Fig. 3).

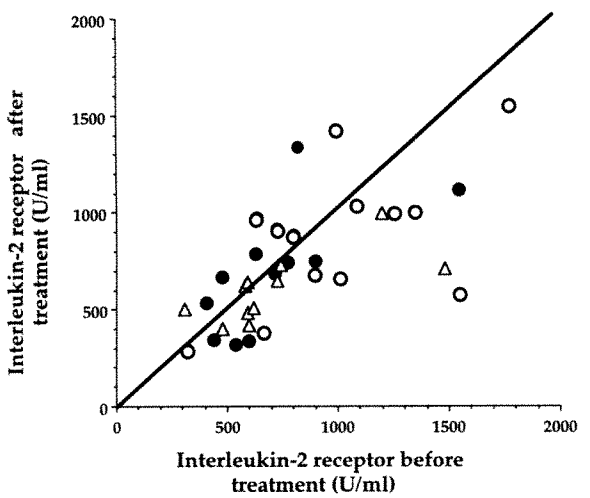


Fig. 3 (BenEzra and associates). Correlation between pretreatment and posttreatment serum interleukin-2 receptor levels in patients with ocular Behçet's disease. Each value represents the level on initial examination and the level detected four to six weeks after treatment with either cyclosporine (open circles) only, corticosteroids (triangles) only, or a combination of both (filled circles).

Discussion

Although a few of the patients with ocular Behçet's disease had a pretreatment serum interleukin-2 receptor level within the normal range, 66.7% had a serum level higher than the normal mean + 2 standard deviations at initial examination. In patients with intermediate uveitis, the mean serum interleukin-2 receptor level was within the normal range, and is comparable with the data obtained by other investigators[13] and by our group during an earlier pilot study.[18] These findings may reflect the localization of immune activation to the eyes in isolated endogenous uveitis. In ocular Behçet's disease, the uveitis is accompanied by systemic immune manifestations, which induce the higher levels of interleukin-2 receptor in the serum.

Initially, most patients with ocular Behçet's disease had a marked decrease of their intraocular inflammation after treatment with cyclosporine, methylprednisolone, or a combination of both.[16] A good correlation between the decrease of serum interleukin-2 receptor and the response to treatment with cyclosporine was found in a group of patients with Crohn's disease.[19] In our group of patients with ocular Behçet's disease, however, the changes in serum interleukin-2 receptor levels after treatment

depended on the initial serum interleukin-2 receptor level of the patient. When the serum pretreatment levels were lower than 800 U/ml, only minimal changes in levels were observed after four to six weeks of treatment. Conversely, all patients (but one) with pretreatment levels higher than 800 U/ml had a decrease of the levels four to six weeks after treatment. Among these patients, the interleukin-2 receptor level decreased to within the normal range in only one.

The highest percentage of patients (45.5%) with ocular Behçet's disease with a low degree of intraocular inflammation was found among those patients with a serum interleukin-2 receptor level of 500 U/ml or lower, whereas 75% of the patients (nine of 12) with severe intraocular inflammation had a serum level of more than 1,000 U/ml. Attempts to correlate the serum interleukin-2 receptor levels with other systemic manifestations (aphthous stomatitis, genital ulcers, arthritis, or erythema nodosum) of ocular Behçet's disease or with the presence or absence of HLA-B51 were noncontributory.

We also tested the serum interleukin-2 receptor levels in patients with other uveitic entities. Four patients with sympathetic ophthalmia and six patients with birdshot choroidopathy or diffuse inner punctate choroidopathy all had serum interleukin-2 levels within the range of the control group. Conversely, two patients with Vogt-Koyanagi-Harada disease had levels higher than the mean in sera of patients with intermediate uveitis (540 and 690 U/ml).

Because ocular Behçet's disease is essentially diagnosed on the basis of clinical observations, we hope that the serum interleukin-2 receptor levels may be used as an adjunct laboratory test for a better differential diagnosis of this disease and other uveitic conditions with quiescent underlying systemic autoimmune manifestations, as in Vogt-Koyanagi-Harada disease and juvenile rheumatoid arthritis.

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Determination of Corneal Image-forming Properties From Corneal Topography

Robert K. Maloney, M.D., Stephen J. Bogan, M.D., and George O. Waring III, M.D.

Keratometry provides useful information about the cornea's image-forming properties, such as corneal astigmatism, but is inaccurate on irregular corneas. Quantitative corneal topographic information is now obtainable on irregular corneas, but is difficult for the clinician to interpret. We developed a method to determine the spherical power, astigmatism, and topographic irregularity of a cornea by finding the best-fit spherocylinder that was closest to its measured topography. Keratometric measurements and two videokeratographs were gathered prospectively on 262 normal and abnormal corneas. The best-fit measurements of spherical power, astigmatism, and topographic irregularity were reproducible with one standard deviation of 0.75 diopter or better; agreement with keratometric measurements in normal eyes was good (0.60 diopter or better). Topographic irregularity averaged 0.1 diopter on precision spheres, 0.4 diopter on 146 normal eyes, 0.8 diopter on 29 eyes after radial keratotomy, 2.0 diopters on 58 eyes after penetrating keratoplasty, and 3.0 diopters on 29 eyes with advanced keratoconus. We conclude the following: basic corneal image-forming properties can be measured from videokeratographs; the properties can be determined, by our methods, on irregular corneas in which keratometry is unreliable; and topographic irregularity provides a measure of irregular astigmatism.

THE SHAPE of the anterior corneal surface largely determines the quality of the retinal image, because this surface determines the shape of the tear-air interface, the most powerful image-forming interface in the eye. Focusing errors of the corneal surface, such as regular corneal astigmatism, degrade the retinal image. An error in corneal spherical power or astigmatism is easily correctable with spectacles. Optical aberrations of the cornea, such as coma and distortion, are not correctable with spectacles.[1(p.211)] Such aberrations, usually called irregular astigmatism, are common in keratoconus and after penetrating keratoplasty, and can develop after radial keratotomy and other refractive corneal surgical procedures. It would be useful to have a method of measuring corneal shape that could separate focusing errors that are correctable with spectacles from irregular astigmatism that is not.

The keratometer can measure corneal spherical power and astigmatism, but it does so at only four points in two perpendicular meridians.[2] On irregular corneas, these measurements are unreliable. The keratometer also provides only a crude, qualitative measure of irregular astigmatism, judged by distortion of the mires.

Much more information about corneal shape, or topography, can be obtained by videokeratography, which provides a detailed depiction of the corneal surface.[3] Maguire, Singer, and Klyce[4] introduced the color dioptric map for displaying corneal topography.[4] Each measured point on the cornea is represented by its curvature, in diopters, in a radial direction. The color dioptric map is an important advance, because it allows visual inspection of optical zone size,[5] centration,[6] and regularity.[7]

Although the color dioptric map provides a quantitative power at each point, interpretation of the pattern of colors is qualitative: the user inspects the map and attempts to ascertain the optical properties of interest. This limits the usefulness of the color dioptric map. The map provides information only about individual points on the cornea, but the retinal image is a composite of light refracted by all points on the cornea that lie over the entrance pupil.[8] The

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From the Emory University Department of Ophthalmology, Atlanta, Georgia. This study was supported in part by Computed Anatomy, Inc., New York, New York; and an unrestricted grant from Research to Prevent Blindness, Inc., New York, New York. Dr. Maloney was a 1989–1991 Heed Ophthalmic Fellow.
Reprint requests to Robert K. Maloney, M.D., Jules Stein Eye Institute, 100 Stein Plaza, UCLA, Los Angeles, CA 90024-7003.

relationship between the dioptric power at each point on the corneal surface and the overall image-forming ability of the cornea is not obvious. In practical terms, it is difficult to look at a pattern of colors in a topographic map and determine whether the corneal shape explains a particular patient's loss in visual acuity or astigmatism.

To understand better the effect of corneal topography on vision, a method is needed to combine the dioptric powers at many points on the corneal surface into overall measures of the cornea's image-forming properties. This approach was first proposed by Dingeldein, Klyce, and Wilson,[9] and Wilson and Klyce,[10] who derived empiric measures from corneal topography. For example, to determine corneal astigmatism, they found the meridian with greatest average power on keratoscope rings 7, 8, and 9, and subtracted the average power of rings 7, 8, and 9 in the perpendicular meridian. This method has the same limitation as keratometry, in that it determines astigmatism at a limited number of points on the cornea. A less empiric and perhaps more intuitive approach to determine corneal spherical equivalent power and astigmatism would be to find the spherocylindrical lens that is closest in shape to the cornea: the best-fit spherocylindrical lens.[11] The spherical equivalent power and astigmatism of the best-fit lens might provide the best estimate for the spherical equivalent power and astigmatism of the cornea in question. In our study, we used a method to determine the best-fit spherocylindrical lens from the topographic map of a cornea, and to derive its spherical power and astigmatism. We also used a method to estimate quantitatively the cornea's irregular astigmatism. We then tested these measures on normal and abnormal corneas.

Subjects and Methods

Study population—Three hundred ninety-nine eyes of 212 subjects with normal corneas were enrolled in a study to classify normal corneal topography, the results of which have been previously described.[12] A cornea was considered normal and was enrolled in the original study if it met the following criteria: (1) there was no history of ocular surgery, (2) results of slit-lamp examination were normal, (3) the best-corrected visual acuity was 20/100 or better to allow adequate fixation, (4) keratometric mires were regular, and (5) there was no history of contact-lens wear. Manifest refraction, keratometry (Bausch and Lomb keratometer, Bausch and Lomb, Rochester, New York), and videokeratography with the Corneal Modeling System (software version 1.3, Computed Anatomy, Inc., New York, New York) were performed on all enrolled eyes. Both the keratometer and the Corneal Modeling System were calibrated on precision steel test spheres at the beginning of the study, and calibration was rechecked periodically. Four videokeratographs were taken of each eye. The study protocol required selecting the best keratograph for processing, defined as the one with the widest eyelid opening that was well focused and free of dry spots in the tear film. Generally, the second-best second keratograph was also processed.

Of the 399 eyes enrolled in the original study, 11 were excluded because of missing data or incomplete data collection. In subjects in whom both eyes were enrolled, one eye was randomly excluded by computer. One eye each of 215 subjects remained. Eyes in which only a single videokeratograph had been previously processed were excluded. As a result, two processed videokeratographs were obtained from each of 146 normal eyes (146 subjects).

Videokeratographs were also obtained in a similar study of the following three groups of eyes from patients who were seen at our institution and who agreed to videokeratography: (1) eyes after radial keratotomy with or without simultaneous transverse keratotomy; (2) eyes after penetrating keratoplasty; and (3) eyes with keratoconus referred for consideration of penetrating keratoplasty. Eyes without two quality videokeratographs, as defined previously, were excluded from analysis. Both eyes of a single patient were permitted in the analysis. All operated-on eyes had had radial keratotomy at least two months previously. After exclusion, 29 eyes remained after radial keratotomy, 58 eyes remained after penetrating keratoplasty, and 29 eyes remained with advanced keratoconus.

Determination of the best-fit spherocylinder—From the measured corneal topography, the spherocylindrical surface that most closely approximated the cornea was determined mathematically. We used mathematical methods that can be found in any text on vector calculus.[13]

The corneal surface is described in the polar coordinates, $D(r,\theta)$, by the topography system. Here, r is the radius from the center of the

keratograph, which corresponds to the corneal vertex.[6] The theta (θ) is the angle counterclockwise from the 0-degree semimeridian. $D(r,\theta)$ is the dioptric power of the cornea at the point specified by r and θ. The set of all such surfaces is a vector space.

To find the best-fit spherocylinder to a cornea, some method of describing the dioptric power map of spherocylinders is needed. The obvious approach is to write the equation of a spherocylinder as a surface of revolution around two perpendicular axes, then calculate the curvature (which is proportional to the dioptric power) at each point. We found this approach algebraically intractable. Instead, consider an ellipsoid, which is a close approximation to a perfect spherocylinder at its apex, defined by the equation:

$$z^2 + \frac{D_x}{\alpha}x^2 + \frac{D_y}{\alpha}y^2 = 1$$

where x and y define a position on the iris plane and the z-axis is the vertex normal to the cornea.[6] Alpha is the constant of proportionality that relates corneal radius of curvature to dioptric power, and is usually taken to be 337.5 to allow for the refractive effect of the posterior corneal surface. This ellipsoid has a dioptric power at the apex of D_x in the 180-degree meridian and a dioptric power of D_y in the 90-degree meridian. Converting to cylindrical coordinates with $x = r\cos\theta$ and $y = r\sin\theta$ and rearranging:

$$z^2 + \frac{r^2}{\alpha}\left(\frac{D_x+D_y}{2} + \frac{D_x-D_y}{2}\cos 2\theta\right) = 1$$

This equation can differentiated, with θ fixed, to give dz/dr and d^2z/dr^2. If these quantities are substituted into the standard formula for radius of curvature of a surface,[13] and second order and higher terms are discarded, then the dioptric power D of this ellipsoid at any point near its apex is:

$$D(r,\theta) = \frac{D_x+D_y}{2} + \left(\frac{D_x-D_y}{2}\right)\cos 2\theta$$

This ellipsoid is oriented along the x- and y-axes. If it is oriented along the meridian ϕ, its equation is given by:

(1)

$$D(r,\theta) = \frac{D_x+D_y}{2} + \left(\frac{D_x-D_y}{2}\right)\cos 2(\theta-\phi)$$

We consider this as a description of a perfect spherocylinder. Several features of this equation are intuitively appealing. Along any meridian (θ fixed), the dioptric power of the surface is constant, as it should be for a perfect spherocylinder. The dioptric powers of the two principal meridians ($\theta = \phi$ and $\theta = \phi + 90$ degrees) are D_x and D_y, respectively. The equation has two terms. The first represents the spherical equivalent power of the surface, or average power of the two principal meridians. The second term defines a cross cylinder with total astigmatism equal to the difference in power between the two principal meridians. This equation is consistent with the basic optical principle that any spherocylindrical lens can be represented as a combination of a spherical and a cylindrical lens.

Let $D_1(r,\theta)$ and $D_2(r,\theta)$ describe two corneal surfaces. We choose the standard dot product or scalar product:

(2)

$$D_1 \cdot D_2 = \frac{1}{\pi r_o^2}\int_{r\le r_o} D_1(r,\theta)\, D_2(r,\theta)\, r\,dr\,d\theta$$

where r_0 is the radius of the pupil, assumed to be centered in the keratograph. Two corneas D_1 and D_2 are orthogonal if $D_1 \cdot D_2 = 0$. This scalar product gives rise to the natural metric for measuring the norm, or length, of a function D:

(3)

$$\|D\| = \sqrt{D \cdot D}$$

For a given cornea $D(r,\theta)$, we wished to find the spherocylinder $B(r,\theta)$ that is the best fit. By definition, this is the spherocylinder that minimizes the distance to D, with the norm defined in equation 3. Mathematically,

(4)

$\|D-B\|$ is minimized

By simple trigonometry, the set of all spherocylinders defined by equation 1 is a vector subspace. Therefore, the distance to D is minimized by the orthogonal projection of D onto the subspace of spherocylinders. The functions $V_1(r,\theta) = 1$, $V_2(r,\theta) = \sqrt{2}\cos 2\theta$, and $V_3(r,\theta) = \sqrt{2}\sin 2\theta$ form an orthonormal basis of this subspace. The orthogonal projection of D onto this subspace is given by:

$$B = (V_1 \cdot D)V_1 + (V_2 \cdot D)V_2 + (V_3 \cdot D)V_3$$

with the scalar product given in equation 2. Substituting, the best-fit spherocylinder is:

(5)

$$B = S + \tfrac{1}{2}a_x\cos 2\theta + \tfrac{1}{2}a_y\sin 2\theta$$

with

$$S = \frac{1}{\pi r_o^2} \int_{r<r_o} D\,(r, \theta)\, r dr d\theta$$

$$a_x = \frac{4}{\pi r_o^2} \int_{r<r_o} D\,(r, \theta) \cos 2\theta\, r dr d\theta$$

$$a_y = \frac{4}{\pi r_o^2} \int_{r<r_o} D\,(r, \theta) \sin 2\theta r dr d\theta$$

S is the best-fit spherical power, and is simply the average power of the cornea over the presumed pupil. The magnitudes of the corneal astigmatism are a_x and a_y represented as two crossed cylinders, with a_x oriented at 90 degrees/180 degrees, and a_y oriented at 45 degrees/135 degrees.

Equation 4 can be rewritten in the form of equation 1, which defines a spherocylinder, as:

$B(r,\theta) = S + \frac{1}{2}A[\cos 2(\theta - \phi)]$

with

$$A = \sqrt{a_x^2 + a_y^2}$$

$$\phi = \frac{1}{2} \arctan \frac{a_y}{a_x} \text{ if } a_x \geq 0$$

$$\text{or } \phi = 90 + \frac{1}{2} \arctan \frac{a_y}{a_x} \text{ if } a_x < 0$$

The quantity A is the magnitude of best-fit astigmatism, and ϕ is the meridian of the best-fit astigmatism.

The difference between the cornea $D(r,\theta)$ and the best-fit spherocylinder $B(r,\theta)$ yields a difference topography map. As discussed previously, B is the spherocylinder closest to D, as defined by equation 4. We define topographic irregularity as the distance between these surfaces:

$$TI = \|D - B\|$$

Expanded, this is:

$$TI = \sqrt{\frac{1}{\pi r_o^2} \int_{r<r_o} [D\,(r, \theta) - B\,(r, \theta)]^2\, r dr d\theta}$$

TI has units of diopters. It is defined so that the topographic irregularity of a perfect spherocylinder is 0, and a poorer fit leads to greater topographic irregularity.

In practice, all integrals in the previous formulas are replaced with finite sums; the root mean square integral for topographic irregularity becomes a root mean square sum.

Best-fit topographic measures—The best-fit spherocylinder was fitted to the central 4-mm-diameter circle at the center of the videokeratograph to approximate the size and location of the entrance pupil. The best-fit spherical power of the measured cornea was defined as the spherical equivalent power of the best-fit spherocylinder. Best-fit astigmatic power was defined as the power of the (plus) cylinder portion of the best-fit spherocylinder. Best-fit astigmatic meridian was defined as the steepest meridian of the best-fit spherocylinder. The difference between the cornea and the best-fit spherocylinder was calculated at each measured point. The root mean square sum of all of these differences was defined to be the topographic irregularity of the measured cornea.

Algorithms were implemented in the Pascal language and run on the 80286-based processor in the Corneal Modeling System. These algorithms allowed the user to identify any keratograph and calculate the best-fit quantities listed previously. They also allowed the generation of a topographic map of the best-fit spherocylinder, and a topographic map of the difference between the cornea and its best-fit spherocylinder. Each of these measures (best-fit spherical power, astigmatic power and meridian, and topographic irregularity) was calculated for each videokeratograph.

Data analysis—The reproducibility of each measure was determined by comparing its values on the two different videokeratographs of each cornea. For example, to determine the reproducibility of best-fit spherical power (the spherical equivalent power of the best-fit spherocylinder) on normal corneas, the signed difference between the first and second videokeratographs was determined for each normal cornea. The mean and standard deviation of these differences were calculated for all normal corneas. The mean of the signed differences was expected to be close to zero unless a systematic bias was present between the first and second videokeratographs; it was 0.002 diopter. The standard deviation provided a measure of the average difference between the best-fit spherical power of the two keratographs. The reproducibility of best-fit astigmatic power, meridian, and topographic irregularity was determined in the same manner on each group of corneas. All mean differences were less than 0.13 diopter or 0.8 degree.

The accuracy of these measures was determined by comparing them to keratometric measurements in normal eyes. For best-fit spherical power, the difference between the best-fit power and the average (two meridians) keratometric power was determined for each

keratograph. The mean and standard deviation of the signed differences were calculated. The accuracy of best-fit astigmatic power and meridian was determined in the same manner.

Results

Sample cases—For every cornea, both normal and abnormal, the spherocylinder was determined that most closely approximated the topography of the central 4 mm of the cornea. Figure 1 illustrates how the best-fit spherocylinder allows determination of best-fit spherical power and astigmatism. It shows a normal spherical cornea and its best-fit spherocylinder, which is a perfect sphere, and a normal cornea with regular astigmatism and its best-fit spherocylinder.[12,14]

Once the best-fit spherocylinder of a cornea has been found, topographic irregularity can be determined. Topographic irregularity can be conceptualized as the space between the cornea and its best-fit spherocylinder (Fig. 2). If there is little space, the fit is good and the cornea is regular. If the space is large, the fit is poor and the cornea is irregular. The value of the best-fit topographic measures is illustrated in Figure 3, which shows two eyes with keratoconus.

The algorithms for determining best-fit spherical power, astigmatic power, and astigmatic meridian were validated by applying them to mathematically generated perfect spherocylindrical surfaces. On such surfaces, the accuracy of the algorithms was better than 0.05 diopter for spherical and astigmatic power, and better than 0.5 degree for the astigmatic meridian.

Reproducibility of best-fit topographic measures—Reproducibility of each best-fit measure was assessed by comparing the values from the two keratographs for each eye. If best-fit spherical power, for example, were perfectly reproducible, the two keratographs in a pair would always have the same best-fit spherical power.

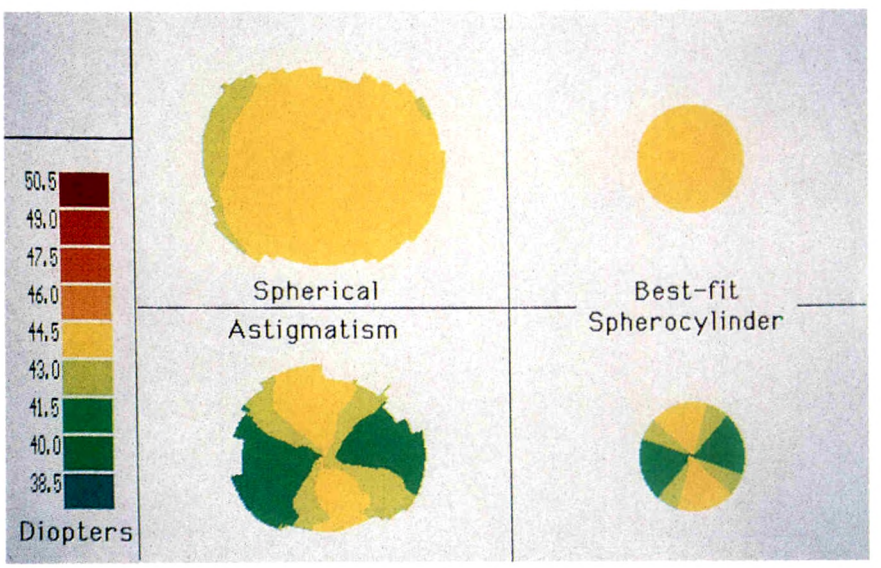


Fig. 1 (Maloney, Bogan, and Waring). Normal spherical and astigmatic corneas. Top left, A normal eye with a manifest refraction of −0.25 sphere and a keratometric power of 44.75 sphere. The corneal topographic map discloses a spherical central cornea and normal aspheric flattening toward the periphery. Top right, Its best-fit spherocylinder is a perfect sphere, with a uniform power of 44.6 diopters. No aspheric flattening is present in a perfect sphere. The map of the best-fit sphere is 4 mm in diameter, corresponding to the presumed entrance pupil. Bottom left, A normal eye with regular astigmatism. The keratometric power is 41.75/45.50 × 103 degrees, and the manifest refraction has +3.75 diopters of astigmatism at 105 degrees. The corneal topography has the characteristic bow-tie shape of regular corneal astigmatism. Bottom right, The best-fit spherocylinder has a flat meridian of 41.1 diopters at 15 degrees, and a steep meridian of 44.7 diopters at 105 degrees. This yields a best-fit spherical power of 42.9 diopters, and a best-fit astigmatism of +3.6 diopters × 105 degrees. The best-fit spherocylinder has a propeller-shaped pattern because the dioptric power of a perfect spherocylinder does not change along a given semimeridian. The bow-tie shape is produced in astigmatic corneas by the effect of normal aspheric flattening on the propeller shape.

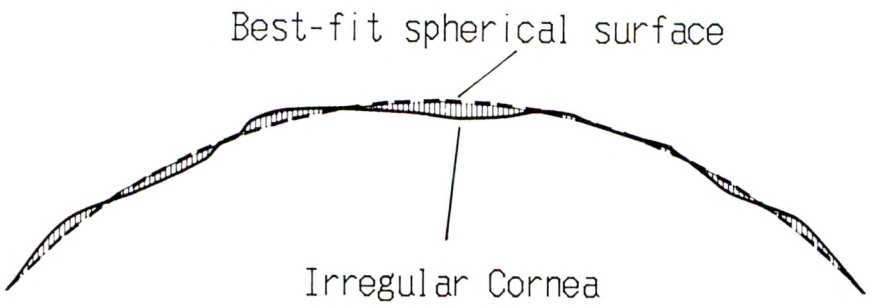


Fig. 2 (Maloney, Bogan, and Waring). Determination of topographic irregularity. The irregular cornea (wavy line) is approximated as closely as possible by the best-fit spherocylinder (dashed arc). The amount of space between the two curves (hatched) is intuitively a measure of how much the cornea deviates from a perfect spherocylinder. Topographic irregularity is a measure of this space.

In normal eyes, the standard deviation of the signed differences between the two keratographs was 0.25 diopter, so two thirds of the paired keratographs would be expected to agree within 0.25 diopter for best-fit spherical power. The reproducibility of best-fit spherical power, astigmatic power and meridian, and irregularity in normal and abnormal eyes is shown in Table 1. The best-fit topographic measures were less reproducible in abnormal eyes, presumably because the videokeratographs were less reproducible on irregular corneal surfaces.

Accuracy of best-fit topographic measures—The accuracy of the best-fit topographic measures was assessed in normal eyes by comparing each one to the appropriate keratometric measurement. No assessment of the accuracy of the best-fit topographic measures was attempted in abnormal eyes, because keratometric measurements were believed to be too inaccur-

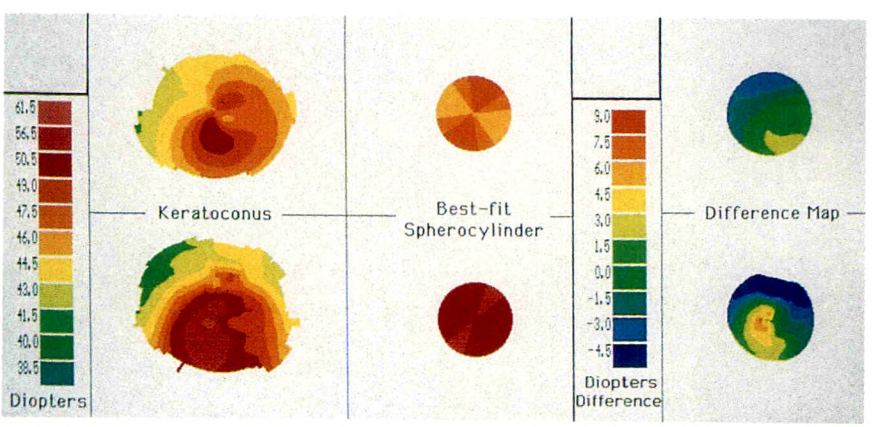


Fig. 3 (Maloney, Bogan, and Waring). Top and bottom left, The topography of two corneas with keratoconus. It is not apparent by inspection of the topographic maps which cornea has better manifest visual acuity or greater astigmatism. Top left, Keratoconic cornea with a manifest visual acuity of 20/25 with a manifest refraction that has 2.5 diopters of cylinder at axis 60 degrees. The corneal astigmatism is apparent as a distorted, obliquely oriented bow tie in the color map. Bottom left, Keratoconic cornea with a manifest visual acuity of 20/60 with a refraction that also has 2.5 diopters of cylinder at 60 degrees, yet the color map does not disclose bow-tie astigmatism. Top and bottom center, The best-fit spherocylinders of these corneas. The best-fit astigmatism of the top cornea is +3.4 diopters × 66 degrees, and of the bottom cornea is +3.6 diopters × 56 degrees. The correlation with manifest astigmatism is good in both cases. The best-fit topographic measure detects astigmatism in the bottom cornea that is not apparent on inspection of the topographic map, but is present by manifest refraction. Top and bottom right, Topographic irregularity of these corneas, obtained by subtracting the best-fit spherocylinder from its respective color dioptric map. Each map discloses the local irregularities in the cornea; at each point, the color value represents how much the cornea deviates from the best-fit spherocylinder. Top right, Deviations range from −3.0 to +3.0 diopters, and the topographic irregularity is 1.7 diopters. Bottom right, The cornea is considerably more irregular, with deviations from −4.5 to +7.5 diopters, and a topographic irregularity of 3.3 diopters. The topographic irregularities correspond well to the manifest visual acuities.

TABLE 1
REPRODUCIBILITY OF BEST-FIT TOPOGRAPHIC MEASURES*

BEST-FIT MEASURE	EYES WITH NORMAL CORNEAS (N = 146)	EYES AFTER RADIAL KERATOTOMY (N = 29)	EYES AFTER PENETRATING KERATOPLASTY (N = 58)	EYES WITH KERATOCONUS (N = 29)
Spherical power (diopters)	0.25	0.21	0.72	0.34
Astigmatic power (diopters)	0.15	0.26	0.66	0.31
Astigmatic meridian (degrees)	5	9	8	7
Irregularity (diopters)	0.16	0.14	0.66	0.19

*Values shown are the standard deviation of the signed differences between paired keratographs. Sixty-seven percent of the measurements on pairs of keratographs would be expected to fall within the indicated values.

ate in this group of eyes. A scatterplot of average keratometric power vs best-fit spherical power (Fig. 4) shows that best-fit spherical power underestimated keratometric spherical power by an average of 0.25 diopter. Two thirds of the measurements of best-fit spherical power would be expected to be within 0.60 diopter of the keratometric value. In some eyes, there was a large difference between the best-fit spherical power and the average keratometric power. We could find no errors in the videokeratographs in these eyes, which seemed to be properly centered, focused, and processed. These large differences may represent errors in recording of the keratometric measurements.

Best-fit astigmatic power was compared to keratometric astigmatic power in an identical manner (Fig. 5). No consistent errors in estimating astigmatism were present. Two thirds of the measurements of best-fit astigmatic power would be expected to be within 0.37 diopter of the keratometric values.

Agreement between keratometric and best-fit astigmatic meridians was only fair for low amounts of astigmatism, possibly because the orientation of the keratometric meridian is relatively imprecise for low amounts of astigmatism. To attempt to improve the accuracy of the keratometric meridian measurement, eyes with less than 0.75 diopter of keratometric astigma-

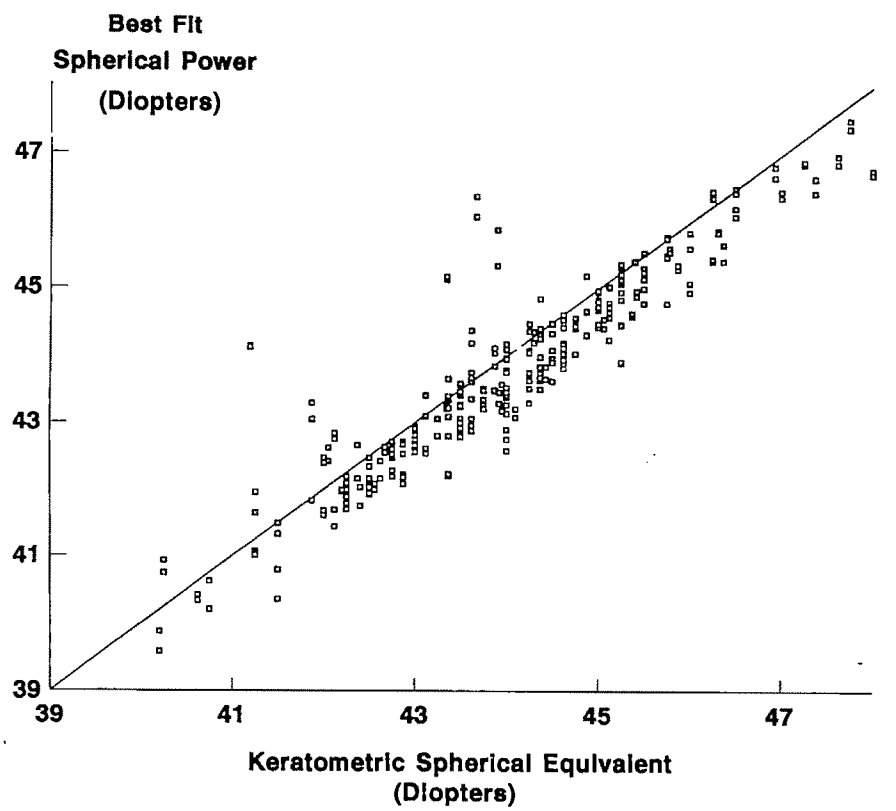


Fig. 4 (Maloney, Bogan, and Waring). Keratometric spherical equivalent and best-fit spherical power. For each normal cornea, average keratometric power is plotted on the horizontal axis and the best-fit spherical power of its two keratographs is plotted on the vertical axis. If the agreement between keratometric and topographic measures were perfect, all points would lie on the diagonal line. Best-fit spherical power averages 0.25 diopter less than the spherical equivalent keratometric power.

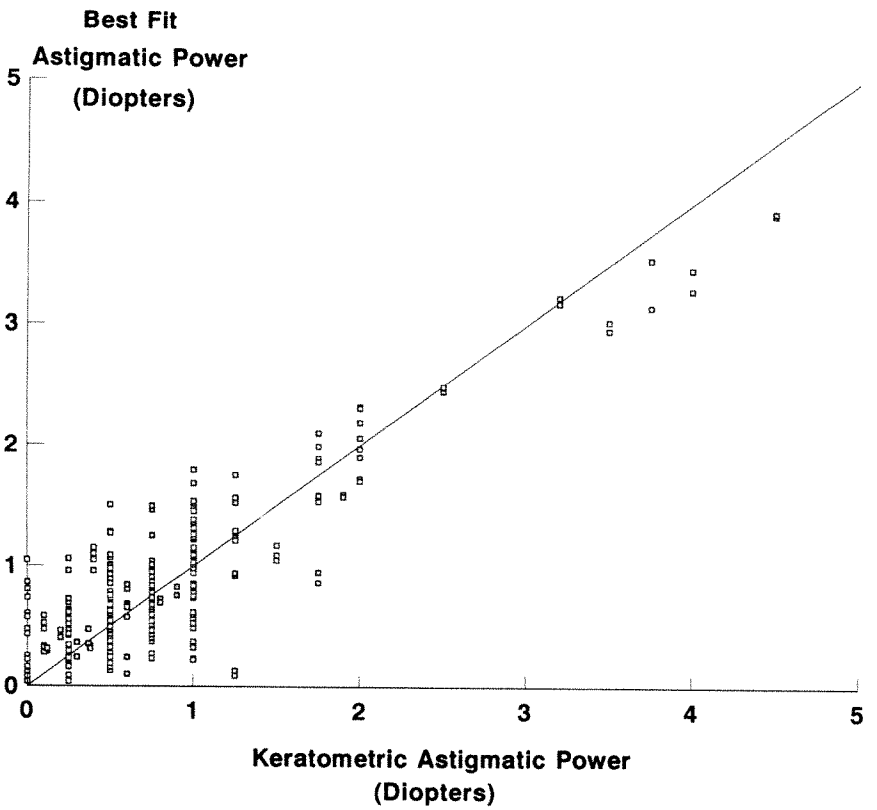


Fig. 5 (Maloney, Bogan, and Waring). Keratometric astigmatic power and best-fit astigmatic power. For each normal cornea, the difference between the steep and flat keratometric meridians is plotted on the horizontal axis, and the best-fit astigmatic power of its two keratographs is plotted on the vertical axis. No consistent errors are present.

tism were excluded. The location of the best-fit astigmatic meridian was compared to the steep keratometric meridian in this subset of eyes (Fig. 6). Two thirds of the best-fit meridian measurements would be expected to be within 11 degrees of the keratometric meridian.

No standard was available to judge the accuracy of the topographic irregularity measure. Irregularity is generally assessed qualitatively by the presence of distortions in the keratometric mires. Instead, the measure for topographic irregularity was tested on different groups of corneas in which the qualitative irregularity was known in general. The topographic irregularity of a precision sphere is 0.1 diopter, a measure of the inherent noise in the Corneal Modeling System. Qualitatively, the clinical estimate of the relative irregularity of the following groups of corneas increases progressively: normal eyes, eyes on which radial keratotomy has been performed, eyes on which penetrating keratoplasty has been performed, and eyes with advanced keratoconus referred for penetrating keratoplasty. The measured topographic irregularity of these groups of eyes increased in the same order (Table 2).

Discussion

Ideal topographic measures—We suggest that topographic measures of the cornea's image-forming properties should meet the following four criteria:

1. The topographic measures should be clinically useful in understanding corneal optical properties. Measures such as spherical power, astigmatism, or irregularity are immediately useful. For example, topographic spherical power may be more accurate than mean keratometric power in choosing an intraocular lens power on eyes on which cataract extraction is performed after penetrating keratoplasty.

2. The topographic measure should be derived in a straightforward manner from basic optical principles. The refraction of light is well understood. If the positions, shapes, and indices of refraction of the various components of an eye were known, then the retinal image could be determined exactly.[1(p.223),15] A topographic measure built on a sound optical foundation is more likely to be valid and more likely to produce reasonable results outside of the

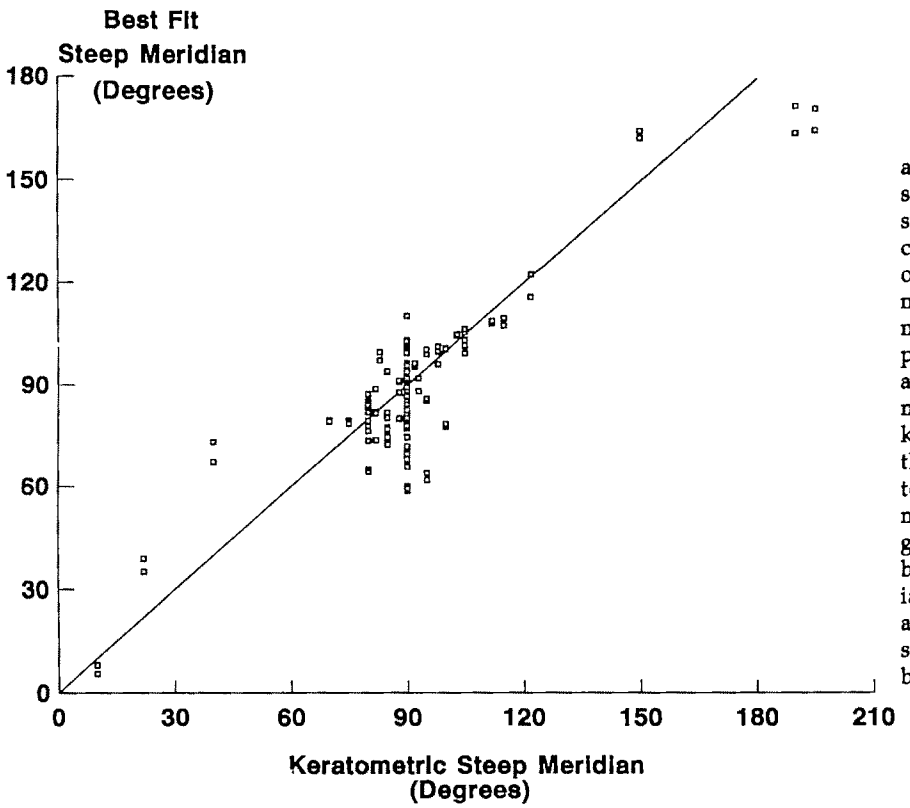


Fig. 6 (Maloney, Bogan, and Waring). Keratometric steep meridian and best-fit steep meridian. For normal corneas with at least 0.75 diopter of keratometric astigmatism (70 eyes), the keratometric steep meridian is plotted on the horizontal axis, and the best-fit astigmatic meridians of its two keratographs are plotted on the vertical axis. Many keratometric meridian measurements fall at exactly 90 degrees, suggesting an observer bias toward labeling meridians that are near 90 degrees as exactly 90 degrees. No such bias is present in the best-fit meridians.

limited domain in which it is tested. For example, the Sanders-Retzlaff-Kratz formula for the calculation of intraocular lens power was derived by regression analysis, and proved to be less accurate than sophisticated optical derivations in eyes with unusual axial lengths.[16] Topographic measures based on statistical methods or on ad hoc assumptions may be inaccurate.

3. The topographic measures should correlate with standard clinical measures in normal eyes. For example, a measure of astigmatic power should agree with the keratometric astigmatic power in normal eyes. This agreement provides some reassurance that the measure is still valid when applied to irregular corneas in which keratometry readings are problematic.

4. The topographic measures should incorporate the topography of all points on the cornea that overlie the entrance pupil and from none outside the entrance pupil. The cornea outside the entrance pupil provides mechanical support and a source of cells, but does not contribute to the foveal image; therefore, points from these areas should not be included in a measure of optical performance. Similarly, all points within the entrance pupil should be included in the topographic measure. The retinal image is formed by all light rays from the object of regard that enter the entrance pupil. For example, a simple measure of astigmatic power could calculate corneal curvature only in the steepest and flattest meridians. However, Sturm's conoid is composed of light rays from all meridians, so such a measure ignores the contribution to astigmatism of all of the intermediate meridians.

Existing topographic measures—Measures that derive optically useful information from topographic data have been proposed previously.

TABLE 2
TOPOGRAPHIC IRREGULARITY OF NORMAL AND ABNORMAL CORNEAS

DIAGNOSIS	NO. OF EYES TESTED	TOPOGRAPHIC IRREGULARITY (DIOPTERS) (MEAN ± STANDARD DEVIATION)
Precision test spheres	3	0.1 ± 0.01
Normal	146	0.4 ± 0.2
Radial keratotomy	29	0.8 ± 0.4
Penetrating keratoplasty	58	2.0 ± 1.2
Keratoconus	29	3.0 ± 1.6

Dingeldein, Klyce, and Wilson[9] developed topographic measures for centrally weighted average corneal power, cylindrical power and meridian, and corneal irregularity. In their study, these measures correlated well with average keratometric power and the keratometric steep meridian. However, these measures included a large area of cornea outside the pupil, and the measures for astigmatism were limited to the steepest and flattest meridians. The measure of irregularity, the Surface Asymmetry Index, was not based on a sufficiently stringent condition of regularity; it was the sum of the absolute differences between the dioptric power of symmetric points on opposite semimeridians. Any radially symmetric surface has a Surface Asymmetry Index of zero. Consequently, a centered cone in a patient with keratoconus could conceivably be measured as highly regular, even though a large amount of irregular astigmatism would be present. These topographic measures satisfy criteria 1 and 3, but do not satisfy criteria 2 and 4.

Wilson and Klyce[10] developed improved measures to simulate keratometric measurements (Sim K) and for surface regularity (the Surface Regularity Index). Sim K correlated well with actual keratometric measurements on regular and irregular corneas. The Surface Regularity Index was designed statistically to allow for multifocality in corneas; it correlated well with best spectacle-corrected visual acuity. These measures were limited to the central 3 to 4 mm of the cornea. However, Sim K measurements were derived from only three rings in the steepest and flattest meridians. Although Sim K successfully predicted keratometric measurements, it was somewhat limited as a topographic measure, because it sampled the cornea in four small areas and excluded most of the topography inside the entrance pupil. These measures satisfy criteria 1 and 3, and only partially satisfy criterion 4.

Cohen and associates[17] developed the Photogrammatic Index Method, a group of measures for the deviation of the keratoscope ring images from circularity. These measures, such as eccentricity and angularity, could not be compared to keratometry; they included a large area of the cornea outside the entrance pupil; and they generally analyzed data only along one or two meridians at a time. The Photogrammatic Index Method measures were designed to classify corneas into groups with similar topography, rather than to analyze image-forming properties; they do not meet the previously described criteria for topographic measures.

Best-fit topographic measures—Our best-fit topographic measures, best-fit sphere, astigmatism, and irregularity, are simple, optically useful quantities. Their derivation is relatively straightforward. Best-fit sphere is determined by finding the sphere that best fits the cornea's shape. This sphere is easily calculated from the color dioptric map by averaging the dioptric power in the central 4 mm of the cornea. Astigmatic power and meridian are determined, in essence, by fitting a crossed cylinder to the central 4 mm of the cornea. The mathematics of this fitting are more complicated. When the sphere and cylinder have been found, the best-fit spherocylinder has been determined. Optically, the best-fit spherocylinder is a rigorous way to define the spherical power and astigmatism of an irregular surface. How closely this approximates the actual cornea is a measure of how regular the cornea is. A quantitative measure of irregularity is obtained by subtracting, at each point in the central 4 mm, the best-fit spherocylinder's dioptric power from the cornea's dioptric power (Fig. 3). A root mean square sum of all of these differences yields the overall measure of topographic irregularity, much as the standard deviation in statistics yields an average deviation of a population from the mean.

The agreement of the best-fit topographic measures with keratometry was good. In some cases, the best-fit topographic measures may be more accurate. For example, Figure 6 discloses that a notable number of eyes had a measured steep keratometric meridian of exactly 90 degrees. The corresponding best-fit meridians generally varied from 75 to 105 degrees. We suspect that there is an observer bias (digit preference) toward reading keratometric meridians that are close to 90 degrees as exactly 90 degrees.

Ideally, our best-fit topographic measures would be limited to the entrance pupil. Unfortunately, the actual location of the entrance pupil is difficult to determine with current topography systems. Moreover, its size varies with ambient lighting, which is usually different than the lighting used in the topography system. To approximate the entrance pupil, all of our optical measures are limited to the central 4 mm of the cornea, and assume a centered pupil. Our best-fit topographic measures meet criteria 1, 2, and 4, but only partially meet criterion 3.

The best-fit topographic measures provide a useful investigational tool. Best-fit spherical power may be more accurate than keratometry

in choosing an intraocular lens power for cataract extraction behind an irregular cornea. Topographic irregularity can provide a measure of the regularity of the optical zone after excimer laser photorefractive keratectomy, and might be used to compare spherical to aspheric ablations. We have noticed that the ablation zone after photorefractive keratectomy is often oval in shape rather than round, because of preexisting astigmatism. The difference map of Figure 3 may help separate ovality caused by poor laser beam quality from ovality caused by astigmatism by subtracting away the astigmatism. Potentially the most valuable use of the best-fit measures would be to predict visual performance, measured either by Snellen acuity or contrast sensitivity. We did not compare visual acuity to topographic irregularity in this study, because we did not exclude eyes with amblyopia, cataract, or retinal disease. Future studies need to address the relation between topographic irregularity and visual performance.

Ray tracing is an appealing method of analyzing the optics of the cornea, because it allows a direct reconstruction of the retinal image.[16] Eventually, ray tracing may be a more accurate way to predict visual acuity and contrast sensitivity than measures of topographic irregularity. However, to determine spherical power and astigmatism by ray tracing, the best-fit Sturm's conoid must be found, which is a difficult mathematical problem. In the interim, the best-fit topographic measures provide a foundation for assessing an irregular cornea's image-forming properties and for understanding the relation between corneal topography and visual performance.

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Eyelid Involvement in Acanthosis Nigricans

Erich B. Groos, M.D., Mark J. Mannis, M.D., Thomas B. Brumley, M.D., and Arthur C. Huntley, M.D.

We treated a 56-year-old man who had acanthosis nigricans associated with gastric adenocarcinoma and involving the axillae, hands, feet, anus, soft palate, and eyes. The patient developed epiphora from occlusion of the canaliculi with papillomatous lesions. Recognition of the ocular signs of this paraneoplastic syndrome may indicate to the ophthalmologist that the patient should have a thorough oncologic examination.

ACANTHOSIS NIGRICANS is a benign skin disorder consisting of pigmented papillomatous hypertrophy of the epithelium.[1] It may be associpeuated with obesity, insulin resistance, therapeutic drug use, polycystic ovary disease, or a variety of malignancies, particularly adenocarcinomas of the gastrointestinal tract.[2-4] Although it develops most commonly in the intertriginous skin areas such as the axillae, neck, external genitalia, and groin, acanthosis nigricans may involve the entire skin surface, including hands, eyes, mouth, esophagus, vagina, and anus.[5] Ocular and periocular involvement is uncommon and, along with both hand and mouth involvement, presages associated malignancy. We managed a case of acanthosis nigricans associated with gastric adenocarcinoma and involving the axillae, hands, feet, anus, soft palate, and eyes. Our patient had symptomatic epiphora secondary to punctal occlusion from the lesions of acanthosis nigricans.

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From the Departments of Ophthalmology (Drs. Groos and Mannis) and Dermatology (Dr. Huntley), University of California, Davis; and the Napa Valley Eye Group (Dr. Brumley), Napa, California. This study was supported in part by an unrestricted research grant from Research to Prevent Blindness, Inc., New York, New York.

Reprint requests to Mark J. Mannis, M.D., Department of Ophthalmology, University of California, Davis, 1603 Alhambra Blvd., Sacramento, CA 95618.

Case Report

A 56-year-old white man in whom acanthosis nigricans and an associated gastrointestinal carcinoma were diagnosed was referred to the Department of Ophthalmology at the University of California, Davis in January 1992. Clinical signs of acanthosis nigricans had developed approximately one year before the initial examination and were followed by the discovery of gastric carcinoma, which at the time was judged unresectable. The patient underwent chemotherapy from February through November 1991, which was unsuccessful. Subsequently, the tumor was resected, and microscopic examination disclosed malignant cells in the tissue margins. Dermatologic involvement steadily increased to include hands, lips, axillae, anus, buccal mucosa, and eyelids (Fig. 1). The skin had velvety hyperplasia that involved the posterior portion of the neck, the axillae, and the knuckle regions of the hands.

The patient developed persistent epiphora and was referred for ophthalmic examination, which disclosed extensive involvement of the upper and lower eyelids of both eyes, with complete occlusion of all four puncta. Lacrimal probing had been attempted, but did not alleviate his symptoms.

The patient had had several episodes of herpes simplex keratitis in the right eye. He also had a family history of diabetes mellitus and colon cancer. He was not being treated with ocular medications and had no known allergies. His medical problems were all related to the gastric carcinoma as described previously. Medications included dexamethasone elixir for the mouth and perioral skin, and corticosteroid ointment for his skin.

On examination, his best-corrected Snellen visual acuity was R.E.: 20/30 and L.E.: 20/25−2. Ocular motility was normal. The pupils were equal in diameter, round, and reactive. There was diffuse papillomatous hypertrophy of the perioral and periocular skin. The lesions

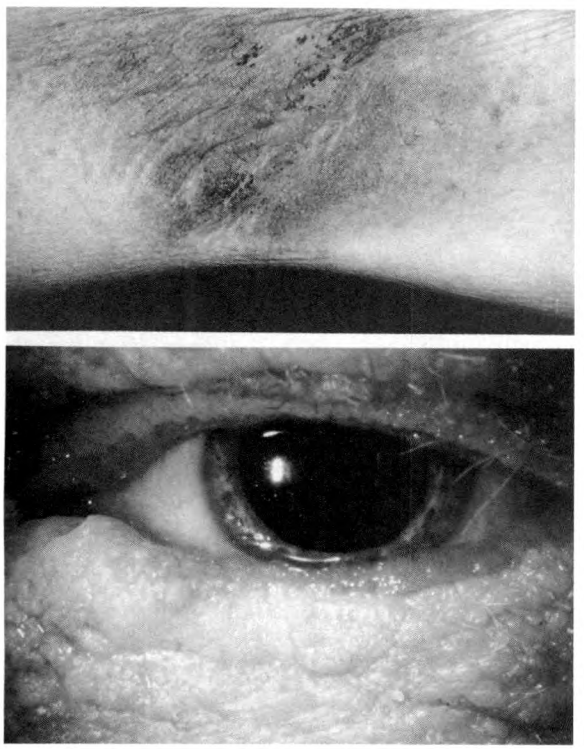


Fig. 1 (Groos and associates). Top, Darkened velvety hyperplasia of axillary skin. Bottom, Eyelid margin covered with the hyperplastic lesions of acanthosis nigricans.

were of waxy consistency, and were verrucous (Fig. 2, top). On both eyelids, the hypertrophic, acanthotic lesions were confluent and obliterated the meibomian gland orifices. A similar process involved the epithelium of the puncta and canaliculi, which effectively occluded both lacrimal drainage systems (Fig. 2, bottom). Papillomatous lesions extended onto the palpebral conjunctivae in both eyes and involved the bulbar conjunctivae deep in the inferonasal fornix. The sclerae in both eyes were normal. There was a branching central scar in the axial portion of the cornea in the right eye; the left cornea was clear. There was obvious epiphora with a generous tear meniscus. The remaining results of biomicroscopic examination were normal in each eye. Intraocular pressures by applanation were 14 mm Hg in the right eye and 13 mm Hg in the left eye. Ophthalmoscopy disclosed normal fundi in both eyes. The eyelid lesions continued to enlarge, causing increasing ocular irritation. The eyelid margins were then debulked by shaving to the surface of the tarsal edge. This provided notable relief of the patient's symptoms. Specimens were submitted

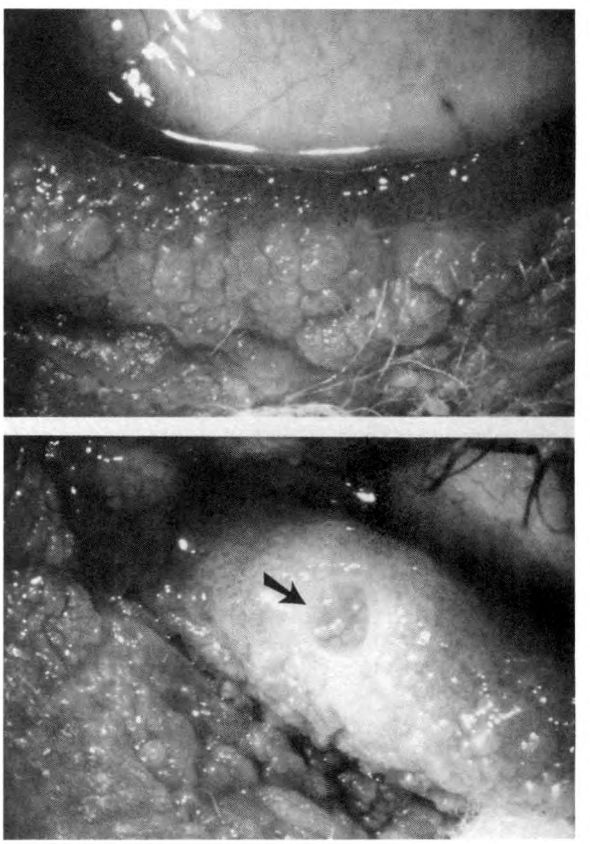


Fig. 2 (Groos and associates). Top, Hypertrophic epithelial changes of the eyelid margin obliterating the meibomian gland orifices. Bottom, Occlusion of the punctal orifice (arrow) with papillary lesions, which completely obstructs the lacrimal drainage system.

for histopathologic analysis. They demonstrated papillary hypertrophy that was consistent with acanthosis nigricans. The patient continues to have epiphora and has had progressive weight loss consistent with progression of the systemic malignancy.

Discussion

Acanthosis nigricans was first described by Pollitzer in 1890.[6] The following two clinical subgroups have emerged: (1) benign acanthosis nigricans, and (2) malignant acanthosis nigricans.[5,7] The benign type may be further subdivided into idiopathic, inherited, endocrine, and drug-related forms.[8] Idiopathic acanthosis nigricans develops in childhood or puberty, is not associated with malignancy or endocrine dis-

ease, and stabilizes or subsides after puberty. It is the most common form of acanthosis nigricans and is frequently but not always associated with obesity. Acanthosis nigricans is associated in some cases with endocrine disorders including type II diabetes mellitus, Addison's disease, Cushing's disease, hyperthyroidism, and hypothyroidism.[2-4] It may also develop with the use of certain drugs, such as nicotinic acid, diethylstilbestrol, corticosteroids, and oral contraceptives.[2,4,9,10] The form associated with malignancy develops first in adult life and may become manifest before, concomitant with, or after the clinical appearance of the associated tumor.[5-7]

The skin manifestations of acanthosis nigricans appear as brown, velvety, hyperkeratic plaques found most often in the flexural areas. Although histologic examination occasionally demonstrates increased melanin in the basal epithelium, hyperkeratosis accounts primarily for the darkened appearance of the skin lesion.[5,8] The lesions are usually symmetric and rarely are generalized.[2,5,7] In the benign forms of acanthosis nigricans, the skin manifestations are usually limited to the flexural areas, whereas malignancies are most commonly associated with extensive skin involvement, including hands, feet, eyes, and mucous membranes.

Ocular involvement in acanthosis nigricans is rare. In 1939, Corrado[11] described involvement of the ocular adnexa in a patient whose first symptoms included ocular irritation, conjunctival hyperemia, and epiphora. His patient had pigmented papillomatous hypertrophy at the eyelid margin that involved the lacrimal drainage system. Obstruction of the lacrimal system was confirmed by dacryocystography. Subsequent studies document verrucous hyperplasia involving the eyelids, but do not document functional ocular involvement.[12] Our case illustrates characteristic ocular involvement and rare canalicular obstruction with epiphora secondary to acanthosis nigricans.

The ocular findings in our patient included hypertrophic papillomas of the eyelid margin that obliterated the meibomian gland orifices, palpebral conjunctival papillomatosis extending onto the globe, and complete upper and lower canalicular obstruction secondary to papillary hypertrophy of the canalicular epithelium.

As in our patient, the skin signs often precede the onset of a clinical malignancy. It is so reliable a predictor of malignancy that its appearance obligates a thorough systemic evaluation for tumor.[5] The development of acanthosis nigricans in this patient directed the examination that would ultimately disclose his gastric adenocarcinoma. Published dermatologic reports demonstrate that gastric adenocarcinoma is the malignancy most frequently associated with acanthosis nigricans. Other malignancies, including malignant lymphoma, squamous cell carcinoma of the cervix and the hypopharynx, bronchial carcinoma, and bronchogenic squamous cell carcinoma, have been associated with this lesion.[5,7,12,13] Involvement of the hands, feet, mouth, and periocular structures strongly indicates potential unidentified malignancy, which should be investigated by an oncologist.[7] As noted previously, benign disorders are more commonly signaled by skin changes in the flexural areas and are associated with obesity, various endocrine disorders, and drug therapy with certain agents.[3,4]

Changes in the skin condition may mirror the disease course of the underlying malignancy, a phenomenon consistent with the description of acanthosis nigricans as a paraneoplastic syndrome.[7,13] Our case illustrates the capability of the dermatosis to improve with chemotherapy and parallel the course of the cancer. Patients with more aggressive neoplasms generally have more extensive skin involvement. The uncertain origin of the skin condition may result from cross-reactivity between tumor antigens and basal epithelial antigens.

Recent attention to ophthalmic paraneoplastic syndromes underscores the potential importance of ophthalmic signs in the diagnosis of systemic disease.[14,15] Acanthosis nigricans is a paraneoplastic syndrome representing the nonmetastatic effect of cancer at sites remote from the tumor. In our case, periocular signs signaled remote, underlying systemic disease. Although there is no local therapy for acanthosis nigricans, the recognition of this ocular finding and its clear implications for the general health of the patient assume importance. Recognition of periocular signs will prompt timely and appropriate involvement of an oncologist in patient care.

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OPHTHALMIC MINIATURE

"Close your eyes, Monsieur! Don't look!"

And with this, he clapped his hands over his eyes.

"What's wrong, my boy?"

"I've been blinded!"

Involuntarily I looked out the window, but my eyes could not stand the blazing light entering the room.

I then realized what had happened. The *Nautilus* had gotten under way and was now traveling at high speed. All the quiet luster from the walls of ice had changed into flashing streaks. The fire from these myriads of diamonds had blended together. The *Nautilus*, propelled by its powerful engines, was traveling through a sheath of lightning.

Then the panels in the lounge closed. We held our hands over our eyes and saw nothing but spots, as if we had been looking at the sun too long. It took our troubled eyes some time to calm down.

Jules Verne, *Twenty Thousand Leagues Under the Sea*
New York, Bantam Books, 1962, pp. 310–311

Orbital Meningoencephalocele Manifesting as a Conjunctival Mass

Andrew Terry, M.D., James R. Patrinely, M.D., Richard L. Anderson, M.D., and Walter Smithwick IV, M.D.

Orbital meningoencephalocele is a rare congenital abnormality caused by a defect of the cranio-orbital bones that usually manifests soon after birth as a soft, cystic fullness in the superomedial canthal area with associated exophthalmos. We managed an unusual case of congenital orbital meningoencephalocele that manifested as a cystic conjunctival mass without proptosis or periorbital changes. Preoperative computed tomographic scans failed to demonstrate a bone defect. After suture ligature of the posterior stalk, excision of the lesion yielded an ependymal cyst surrounded by neuroglial and meningeal tissue and filled with cerebrospinal fluid. The patient had normal results of ophthalmic and neurologic examinations after transconjunctival resection of the lesion after three years of follow-up. An orbital approach may be appropriate for a few selected cases in which no bone defect is found on computed tomography. Orbital meningoencephalocele should be included in the differential diagnosis of isolated congenital conjunctival cystic masses.

ORBITAL MENINGOENCEPHALOCELE is a rare condition that is defined as a cystic herniation of brain and meninges through an orbital bone defect or through a natural foramen.

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From the Ophthalmic Plastic and Orbital Surgery Service, University of Utah, Salt Lake City, Utah (Drs. Terry and Anderson); and the Department of Ophthalmology and Division of Plastic Surgery, Cullen Eye Institute, Baylor College of Medicine, Houston, Texas (Drs. Patrinely and Smithwick). This study was supported in part by an unrestricted grant to Baylor College of Medicine from Research to Prevent Blindness, Inc., New York, New York.

Reprint requests to James R. Patrinely, M.D., Cullen Eye Institute, Baylor College of Medicine, 6501 Fannin, NC-200, Houston, TX 77030.

Meningoencephaloceles typically manifest in infancy as exophthalmos or as a mass, depending on the location of the bone defect.[1-8] The mass is usually located in the medial canthus above the medial canthal tendon or at the side or dorsum of the nose. If the mass is large enough, it will displace the globe laterally and inferiorly. The globe or the mass may pulsate synchronously with the heartbeat. The mass is usually cystic, fluctuant to palpation, easily transilluminated, and may be reduced with gentle pressure. Manual decompression, however, may cause bradycardia, convulsions, or even coma. Crying or coughing may increase proptosis and the size of the mass.

We diagnosed and treated an atypical orbital meningoencephalocele that manifested as an enlarging conjunctival mass.

Case Report

A 1-month-old girl, born two weeks prematurely by an uncomplicated cesarean section, was referred with a medial conjunctival mass of the left eye (Fig. 1). The parents noticed the mass at birth and described a gradual increase in size of the lesion. The child's growth and development were normal for her age.

Examination disclosed a bluish hue in the superior medial aspect of the left upper eyelid. When the eyelid was everted, a 10- to 15-mm bluish cystic mass was seen in the superonasal quadrant of the conjunctival fornix (Fig. 2). The overlying conjunctival epithelium was normal. There were no pulsations or proptosis. The mass was nontender, nonreducible, and had a rubbery consistency. It slightly indented the globe and displaced it laterally into an exotropic position. The remaining results of the ophthalmic examination, including motility, fixation, and pupillary reaction, were normal. Standardized A-scan and B-scan echography of



Fig. 1 (Terry and associates). A 1-month-old girl with a left superomedial subconjunctival mass and secondary left upper eyelid fullness and blepharoptosis.

the mass demonstrated a cystic anterior orbital lesion that did not extend behind the equator of the globe. No bone defects were noted. Axial and coronal computed tomographic scans with 1-mm cuts displayed a cystic, well-demarcated mass in the anteromedial portion of the left orbit, but no bone defects were documented.

The patient underwent exploratory surgery in which the conjunctival fornix was incised over the mass. The cystic mass was easily fixated with a retinal cryoprobe and was meticulously, sharply, and bluntly dissected posteriorly (Fig. 3). A sample of the clear fluid was removed from the lesion and found to have a glucose level of 120 mg/dl by the glucose dipstick technique. This measurement indicated the fluid was cerebrospinal and confirmed the suspicion of an orbital meningoencephalocele. Immunochemical analysis to detect the presence of B_2-transferrin to confirm the identification of cerebrospinal fluid was not performed. There was a continual low flow of the clear fluid, which indicated a communication to the subarachnoid space. The collapsed cyst was dissected posteriorly as far as possible and the pedicle was tied off in a cerclage fashion with a 4-0 silk suture. Two additional sutures were placed in the same manner to imbricate the pedicle, and the collapsed cyst was resected. After resection, no further leakage of fluid was evident. The conjunctiva was closed with a running, interlocking 7-0 chromic gut suture. Ophthalmoscopy with the patient under general anesthesia demonstrated an optic nerve head and fundus that were normal for the patient's age in both eyes.

The patient was treated with prophylactic intravenous ampicillin and gentamicin postoperatively for 72 hours to prevent meningitis. A pediatric neurosurgical consultation recommended to follow up the patient and obtain skull films and a magnetic resonance scan at 5 months of age. If needed, an intracranial repair of the meningoencephalocele at this age would yield a better cosmetic result. She was hospitalized for three days postoperatively without evidence of infection or cerebrospinal fluid leak according to glucose dipstick checks of the tear film. A follow-up magnetic resonance scan performed six months later and clinical examination documented no evidence of brain herniation or cerebrospinal fluid leakage into the orbit. At one year and three years of follow-up, the child continued to be asymptomatic with normal results of ophthalmic and neurologic examinations and no clinical evidence of meningoencephalocele recurrence.

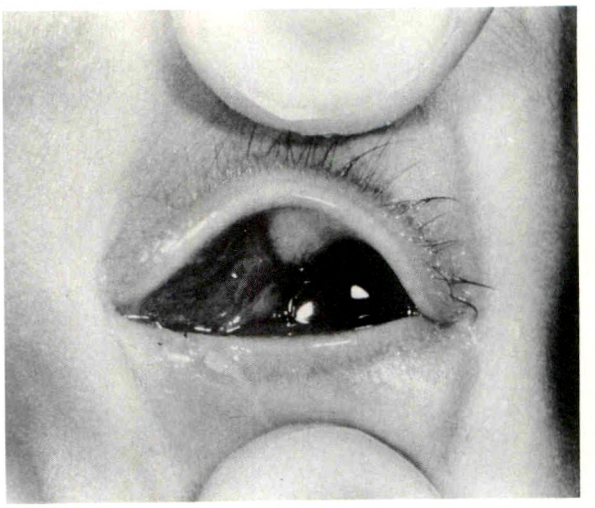


Fig. 2 (Terry and associates). A 10- to 15-mm moderately vascular, reddish blue, cystic mass is seen in the left superonasal quadrant of the conjunctival fornix.

Results

Histopathologically, the tumor was composed of an epithelial-lined cyst surrounded by a thick layer of neuroglial tissue and meninges (Fig. 4). The cyst lining was composed of ependymallike cuboid cells arranged in one to three cell layers. The cyst was surrounded by typical neuroglial fibrillary tissue with widely scattered astrocytes and minimal vasculature. A few isolated calcific bodies were present within the brainlike tissue. In one area, a fibrous meningeallike layer bordered the tumor.

Discussion

Orbital meningoencephalocele is a rare nonhereditary congenital abnormality in which

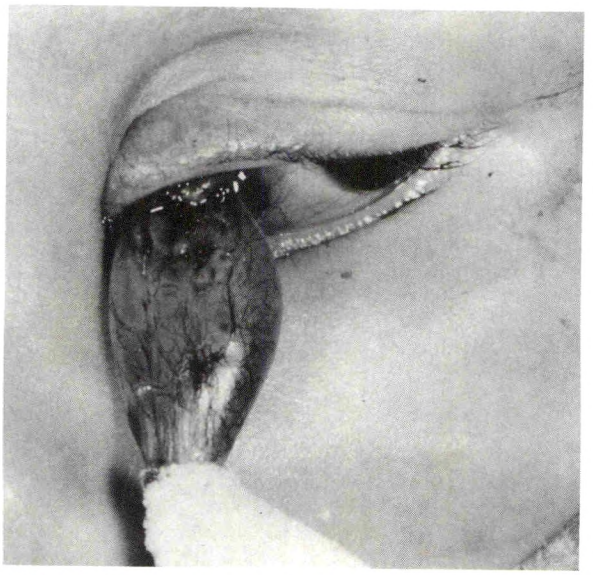


Fig. 3 (Terry and associates). The cystic subconjunctival mass is retracted with a cryoprobe and delivered through a superior fornix incision.

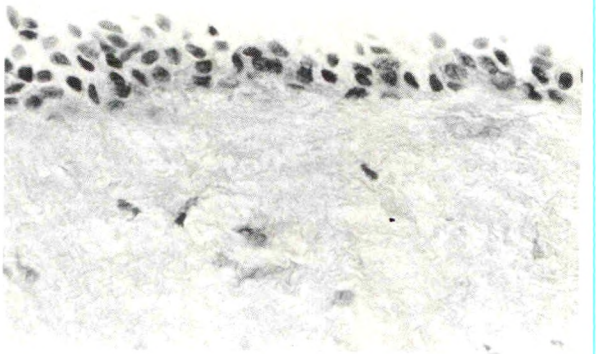


Fig. 4 (Terry and associates). The cyst was lined by several layers of cuboidal epithelial cells and was surrounded by a thick layer of neuroglial tissue and meninges (hematoxylin and eosin, ×400).

meninges, spinal fluid, and brain herniate through a bone defect or, much rarer, through a natural anatomic opening. Orbital meningoencephalocele accounts for less than 1% of orbital masses in children.[10] The anomaly is seldom seen in the western hemisphere, but is frequently found in Thailand, India, Morocco, and Nigeria.[1,9]

If only meninges and cerebrospinal fluid herniate, the lesion is termed a meningocele. When neural tissue is also included in the herniation, the lesion is termed a meningoencephalocele. Some brain tissue is usually present, which may undergo extreme atrophy and degeneration so that true meningoceles are rare. If a ventricle is located within the herniation, the lesion is called a hydroencephalocele.

Orbital meningoencephaloceles are divided into anterior and posterior types. The posterior variety usually manifests in childhood as slowly progressive unilateral proptosis. The meningoencephalocele can herniate through a defect in the orbit or through a natural opening, such as the optic foramen or the orbital fissures. Anterior orbital meningoencephaloceles may be further subdivided into the following three groups depending on the manifestation and the bone defect[1,3]: (1) Nasofrontal types often manifest at the root of the nose with the herniation located between the nasal and frontal bones. These are often associated with ocular hypertelorism. (2) Nasoethmoidal types often manifest at the side of the nose with the herniation occurring between the nasal and ethmoidal bones. (3) Naso-orbital types usually manifest at the inner canthus with the bone defect located between the frontal, lacrimal, and ethmoidal bones. Most orbital meningoencephaloceles are isolated anomalies and do not preclude normal mental and physical development.

Orbital meningoencephaloceles typically manifest with exophthalmos, medial canthal mass, globe displacement, lacrimal sac mass, or ocular hypertelorism.[11] Other ocular anomalies associated with orbital meningoencephaloceles are microphthalmos, colobomas, and anophthalmos.[2,12] Anterior orbital meningoencephaloceles can sometimes be easily diagnosed by the clinical manifestation of a congenital, midline, pulsating, cystic mass that increases in size with crying and may be reduced with gentle pressure. Other manifestations make the clinical diagnosis more difficult. Thin-sliced orbital computed tomographic scans with bone settings are useful for locating the bone defect.[3] Some authors advocate a diagnostic needle aspiration of the cystic mass with chemical analysis of the fluid for confirmation of the diagnosis.[4,12,13] The risk of fistula formation and secondary meningitis are slight with this procedure. Manifestation of an orbital meningoencephalocele as an isolated cystic conjunctival mass, as in our patient, is unique. Although the lesion was suspected preoperatively, thin-cut computed tomographic scans could not document a bone defect or central nervous system communication. Therefore, the diagnosis was made intraoperatively by the confirmation of cerebrospinal fluid within the cyst cavity and continued flow after rupture. The absence of pulsations of the lesion in our patient was not surprising because these lesions may have small

pedicles that do not transmit intracranial pulsations. Ectopic brain tissue, with similar histopathologic features as in our case, may also rarely develop in the orbit.[14,15] In these cases, however, despite the presence of a small bone defect, communication with the subarachnoid system cannot be demonstrated radiographically or intraoperatively. It seems reasonable to assume that meningoencephaloceles and ectopic brain tissue share a similar pathogenesis via herniation of fetal brain tissue, except that subsequent sequestration and discontinuity occur in ectopic brain tissue.

The treatment of orbital meningoencephaloceles usually requires a combined orbital and intracranial approach.[16,17] A sole transorbital repair is usually difficult and unsuccessful.[2] The successful transorbital repair in our case was unusual and may have been aided by the minimal intracranial communication as evidenced by the preoperative computed tomographic scan that disclosed no bone defects.[7] The transfrontal technique, first introduced by Dandy in 1929, is generally considered the ideal approach.[2] Bone defects usually need to be repaired, depending on the size of the defect.[18] Surgical repair is accomplished with a variety of dural flaps and bone grafts. Complications such as meningitis or cerebrospinal fluid leakage may occur and require aggressive treatment.

Orbital meningoencephalocele is a rare condition, but should be suspected in any child with a medial orbital mass, even with normal results of radiologic studies. In rare situations, as in our case, the anomaly may manifest as an isolated conjunctival mass with no observable bone defects and can be corrected by an orbital approach. Orbital meningoencephalocele should be included in the differential diagnosis of congenital conjunctival masses.

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Fluorescein and Indocyanine Green Angiographies of Central Serous Choroidopathy by Scanning Laser Ophthalmoscopy

A. Scheider, M.D., J. E. Nasemann, M.D., and O.-E. Lund, M.D.

We examined 19 patients (41 ± 7.5 years old) with central serous chorioretinopathy and symptoms that ranged from one day to 24 months. Fluorescein and indocyanine green angiographies were performed with a scanning laser ophthalmoscope. Focal exudation was found in all patients with fluorescein and in 15 patients (79%) with indocyanine green. We found a more widespread exudation of indocyanine green into the choroid around the focal hyperfluorescent spot in seven patients (37%). Perfusion with fluorescein was delayed in the area of focal exudation in two patients (11%) and with indocyanine green in 12 patients (63%). Exudation of both dyes stopped with clinical improvement, whereas the perfusion deficits remained unchanged. These results further indicate that central serous chorioretinopathy is primarily a choroidal disease.

CENTRAL SEROUS CHORIORETINOPATHY is characterized by a focal serous detachment of the sensory retina, rarely the retinal pigment epithelium or both layers.[1] Although the clinical features have been extensively described, the exact pathophysiologic aspects of the bleb formation as well as its cause are still unknown. The diagnostic feature is focal leakage of fluorescein through the retinal pigment epithelium, which stops spontaneously or can be sealed with laser coagulation. Although the course of the disease is usually benign, the resultant chorioretinal scar diminishes retinal function,[2] and there is the risk of a secondary development of a subretinal neovascular membrane.[3,4] It has been shown that laser coagulation does not markedly alter the natural course[5] and early treatment of the underlying cause would therefore be necessary to keep the resultant scar as small as possible. Newer pathophysiologic concepts favor a primary origin in the retinal pigment epithelium[6] or in the choroid with secondary involvement of larger portions of the retinal pigment epithelium.[7] Increased exudation from choroidal vessels, induced by ischemia or inflammation, has been suggested as a possible primary cause. Because fluorescein leaks primarily from choroidal vessels, however, an exudation is difficult to demonstrate. The rapid leakage of fluorescein also obscures possible focal areas of ischemia.

Indocyanine green is a tricarbocyane dye with a molecular weight of 775.[8] It binds rapidly and tightly to plasma proteins. The maximum absorption is 790 to 805 nm, the maximum emission is 835 nm.[9] Absorption of its fluorescence by hemoglobin, retinal pigment epithelium, or xanthophyll is minimized because these pigments absorb only a small amount of infrared light.[10]

The almost total binding of indocyanine green to blood protein prevents a marked leakage from fenestrated vessels such as the choriocapillaris, and it therefore allows the detection of small, nonperfused choroidal vascular areas. Hayashi, Hasegawa, and Tokoro[11] used this dye to demonstrate that some patients with central serous chorioretinopathy suffer from focal choroidal ischemia, and that indocyanine green leaks in cases of central serous chorioretino-

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From the Department of Ophthalmology, Ludwig-Maximilians-Universität, München, Germany. This study was supported in part by the Friedrich Baur Stiftung, München, Germany; the Hermann-Wacker Fond, Essen, Germany; and the Wissenschaftsfond der Münchner Medizinischen Wochenschrift, Germany. This study was presented in part at the Third International Symposium on Ocular Circulation and Neovascularization in Paris, France, May 23, 1992.

Reprints request to Dr. med. A. Scheider, Universitätsaugenklinik, Mathildenstr. 8,8000 München 2, Germany.

pathy. They interpreted this leakage as the physiologic exudation of that portion of indocyanine green not bound to protein.

The optical resolution of indocyanine green angiograms was poor at the time of their study, however, and did not permit evaluation of smaller choroidal structures. This situation changed dramatically with the development of the first scanning laser ophthalmoscope that used an infrared laser diode,[12] which permitted the exact imaging of small subretinal neovascular membranes.[13] The most important observation was that exudation from such membranes is uncommon, but it can be induced by laser coagulation.[14] This observation suggested that indocyanine green allows the detection of an abnormal increase in the permeability of choroidal vessels. We therefore studied patients with central serous chorioretinopathy by using an infrared scanning laser ophthalmoscope and indocyanine green.

Patients and Methods

We evaluated the fluorescein and indocyanine green angiograms of 19 consecutive patients with central serous chorioretinopathy. The 18 men and one woman had different stages of the disease. Each patient gave signed consent for the use of indocyanine green angiography. Before angiography, blank images of the fundi were made by using a 1-mm stop and approximately 100 μW of infrared light. This setting allowed an exact imaging of the bleb size with high contrast. For fluorescein angiography 5 ml of a 20% fluorescein solution was injected into the cubital vein and videographic images were recorded by means of scanning argon blue laser ophthalmoscopy (200 μW) on S-VHS tape. Indocyanine green angiography was performed with 25 mg of indocyanine green, dissolved in 2 ml of saline and injected into the cubital vein, followed by 5-ml saline flush. Videographic images were recorded by means of scanning infrared diode laser ophthalmoscopy (1.9 mW) on S-VHS tape. The most important still frames of both angiographies were later digitized and saved on an optical disk.

Angiograms were evaluated for exudation and perfusion deficits. Exudation was rated scant, significant, or massive. Perfusion deficits were defined as an area of delayed, but subsequent complete dye filling. Because of the natural leakage of fluorescein from choroidal vessels, smaller perfusion deficits could not be differentiated from perfusion defects that also slowly filled with the leaking dye. After a deficit had been detected with indocyanine green, we attempted to find a similar angiographic appearance during fluorescein angiography.

Results

The mean age of the 19 patients was 41 ± 7.5 years. The range was 28 to 50 years. The duration of symptoms ranged from one day to 24 months. Exudation of fluorescein was found in all 19 patients. The exudation in six (32%) patients was scant; 11 (58%) showed significant and two (11%) massive exudation. Exudation of indocyanine green occurred in 15 patients (79%). It was scant in two (11%), marked in 11 (58%), and massive in two patients (11%). Exudation of both dyes usually correlated well. Figure 1 demonstrates that even a smokestack phenomenon occurred with indocyanine green. There was no difference in the behavior of both dyes in short-term and long-term cases, but exudation of indocyanine green was often not observed when fluorescein exudation was scant (four of the six eyes with scant exudation). We did not observe indocyanine green exudation without fluorescein exudation. Exudation of indocyanine green stopped before that of fluorescein during the follow-up. In seven patients (37%), we found an area of diffuse indocyanine green exudation into the choroid around the focal hyperfluorescent spot (Fig. 2). A focal perfusion deficit was present in 12 of the 19 patients (63%) with the injection of indocyanine green but only in two (11%) with fluorescein injection (Fig. 3).

Discussion

The clinical features of central serous chorioretinopathy were described more than a century ago by von Graefe.[15] The question of its pathogenesis, however, was initiated by fluorescein angiography. Gass[16] proposed an exudative choroidal reaction of unknown origin as the primary cause of the disease. Wessing[17,18] favored an initial defect in Bruch's membrane or the retinal pigment epithelium. Wessing's concept gained wide acceptance because an

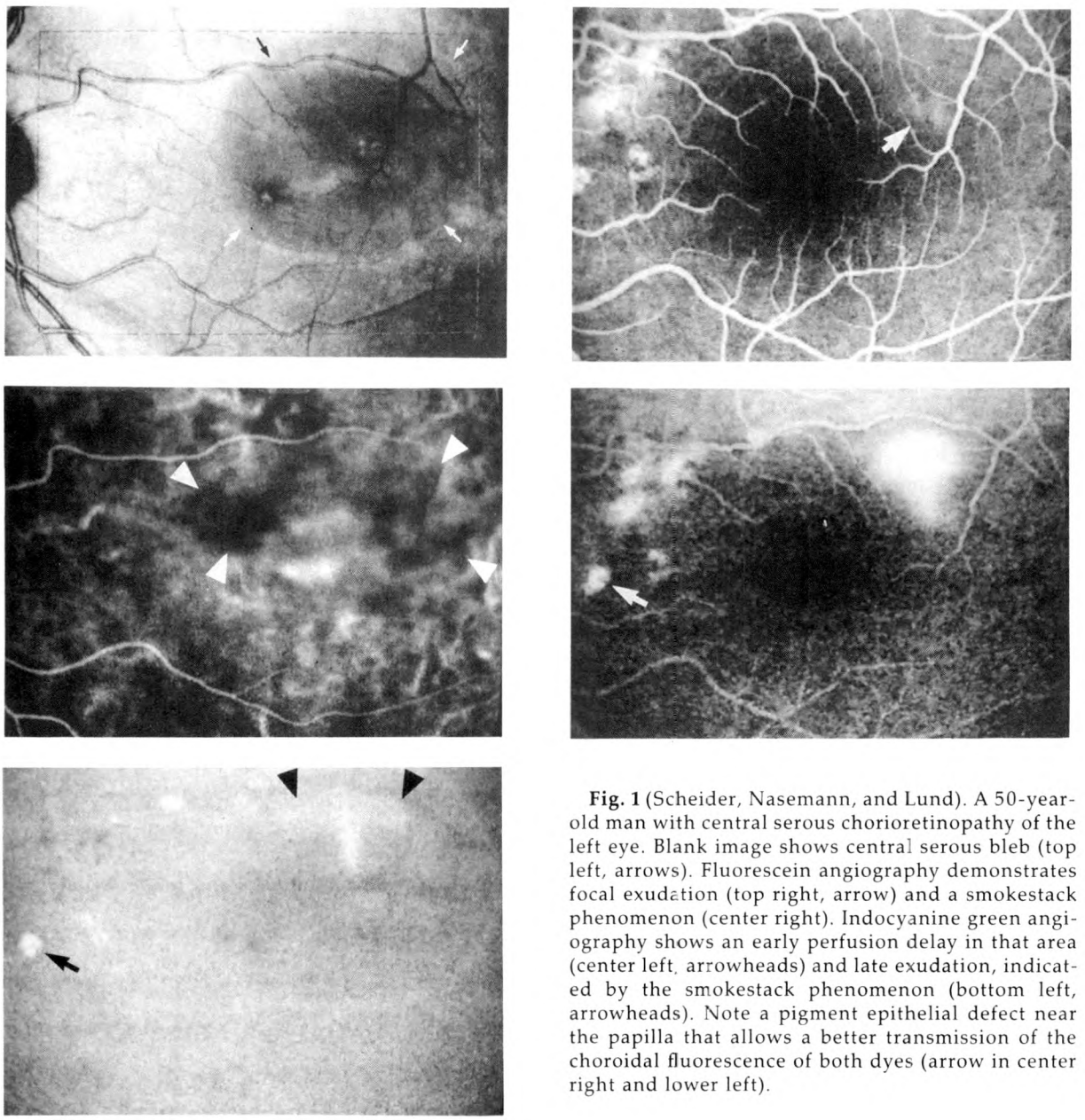


Fig. 1 (Scheider, Nasemann, and Lund). A 50-year-old man with central serous chorioretinopathy of the left eye. Blank image shows central serous bleb (top left, arrows). Fluorescein angiography demonstrates focal exudation (top right, arrow) and a smokestack phenomenon (center right). Indocyanine green angiography shows an early perfusion delay in that area (center left, arrowheads) and late exudation, indicated by the smokestack phenomenon (bottom left, arrowheads). Note a pigment epithelial defect near the papilla that allows a better transmission of the choroidal fluorescence of both dyes (arrow in center right and lower left).

exudative choroidal lesion could not be demonstrated with fluorescein as the dye leaks physiologically from the choriocapillaris. Indocyanine green, however, is almost totally bound to blood protein.[9] Hayashi, Hasegawa, and Tokoro[11] demonstrated indocyanine green leaks from the choriocapillaris in central serous chorioretinopathy. They attributed this exudation to that portion of the dye not bound to protein. If minor exudation occurs physiologically, some indocyanine green should always exude into the choroidal extravascular space and should be detected.

It has been recently shown that indocyanine green does exude only from some subretinal neovascular membranes and only from certain sites.[14] It has been further demonstrated that the dye exudes from previously tight subretinal neovascular vessels after laser coagulation.[14,19] These observations indicate that indocyanine green seems to exude in detectable quantities only in conjunction with its carrier protein.

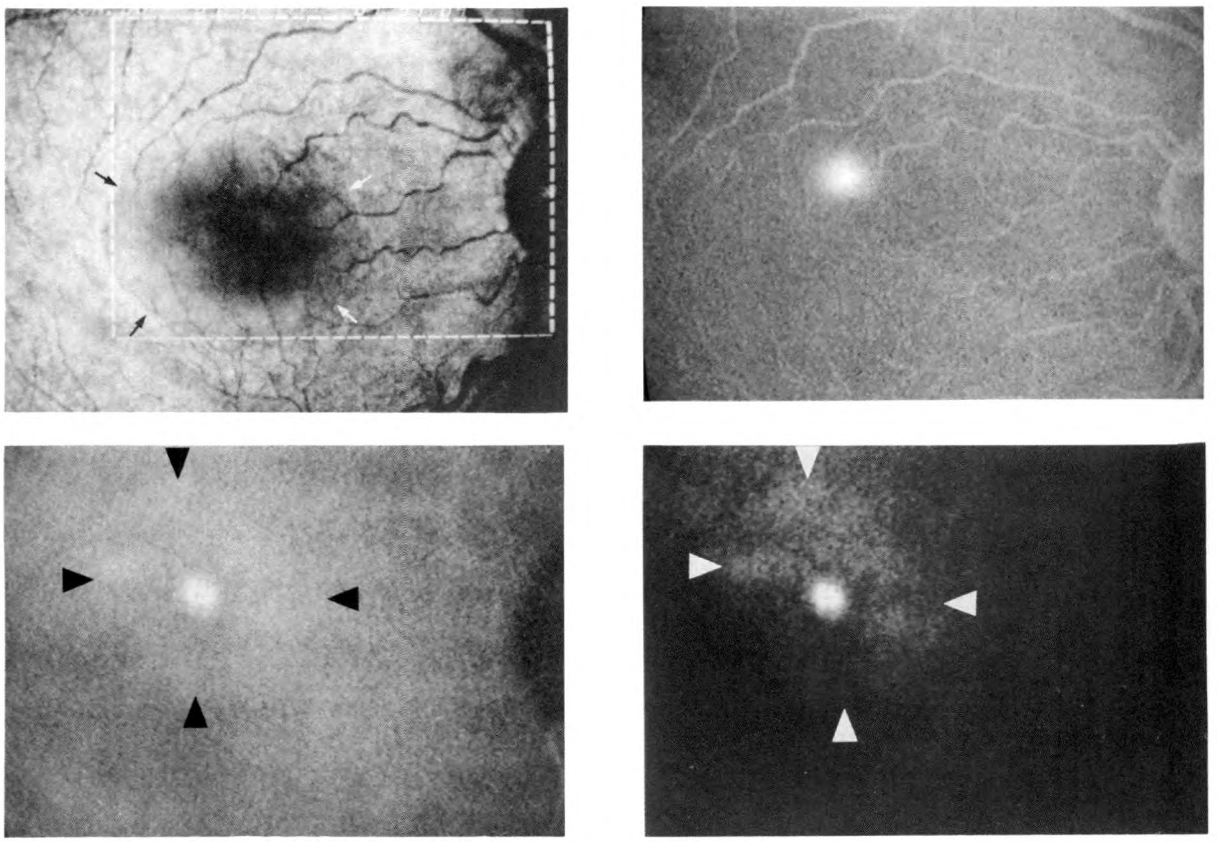


Fig. 2 (Scheider, Nasemann, and Lund). A 35-year-old man with central serous chorioretinopathy of the right eye. Top left, Blank image shows a central serous bleb (arrows). The white frame indicates the region that is displayed during the angiographies. Top right, Fluorescein angiography with spot of intense fluorescence. Bottom left and right, Indocyanine green angiography (after digital intensification shown at right) demonstrates pooling of the dye (arrow) at the same site as fluorescein. Additionally, the spot is surrounded by a larger area of less pronounced hyperfluorescence (arrowheads), indicating a more widespread abnormality.

Thus, choroidal hyperfluorescence of indocyanine green is an important sign of abnormal choroidal vascular hyperpermeability.

We found exudation of indocyanine green in 15 of our 19 patients (79%), which is consistent with the 24 of 30 cases of exudation (80%) Hayashi, Hasegawa, and Tokoro[11] found in their patients. Exudation of indocyanine green was not detectable in four of six patients with scant fluorescein exudation. It is not clear whether there was no exudation of indocyanine green or whether there was too little to be detected with the scanning laser ophthalmoscope. Usually, the amount and size of pooling of both dyes corresponded well. It was usually not possible, however, to decide whether pooling occurred beneath the retinal pigment epithelium or in the subretinal space. Subretinal accumulation was demonstrated with certainty in only one patient with a smokestack exudation of both dyes (Fig. 1). The pooling of both dyes, however, did not occur at the margin of the bleb, but more centrally. Because a pigment epithelial detachment was not observed biomicroscopically or during fluorescein angiography, we believed that the bleb margin consisted of edematous retina.

In addition to this typical dye pooling, in seven of the 19 patients (37%) we detected a larger area of less intense fluorescence surrounding the spot of intense hyperfluorescence that was smaller than the serous retinal detachment and clearly confined to the choroid. Hayashi, Hasegawa, and Tokoro[11] described similar areas in 21 of their 30 cases (70%). They stated that these zones corresponded to retinal pigment epithelium changes in fluorescein angiography. Defects of the retinal pigment epi-

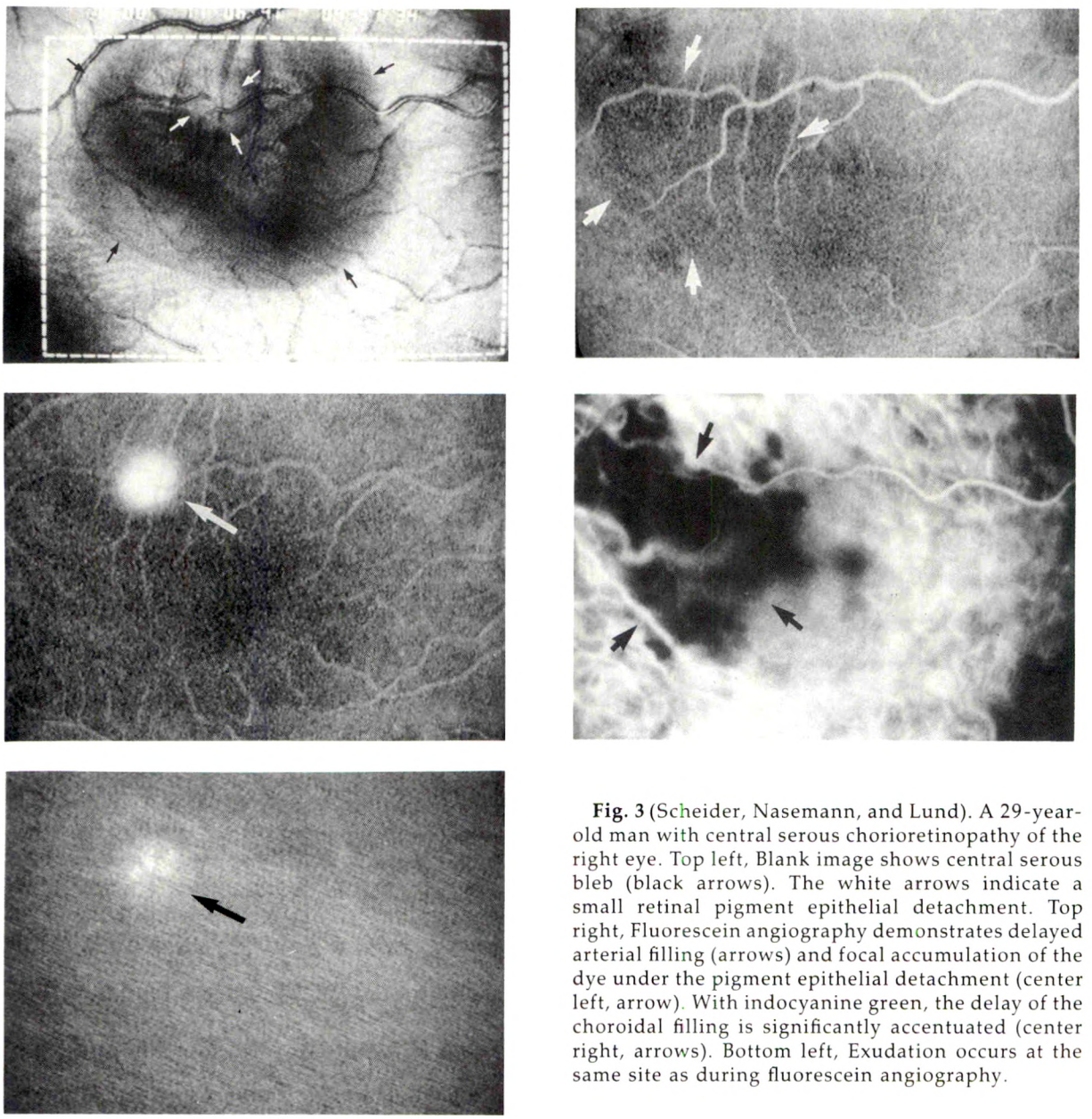


Fig. 3 (Scheider, Nasemann, and Lund). A 29-year-old man with central serous chorioretinopathy of the right eye. Top left, Blank image shows central serous bleb (black arrows). The white arrows indicate a small retinal pigment epithelial detachment. Top right, Fluorescein angiography demonstrates delayed arterial filling (arrows) and focal accumulation of the dye under the pigment epithelial detachment (center left, arrow). With indocyanine green, the delay of the choroidal filling is significantly accentuated (center right, arrows). Bottom left, Exudation occurs at the same site as during fluorescein angiography.

thelium may be the cause of hyperfluorescence during indocyanine green angiography because retinal pigment epithelium blocks 10% of the infrared light.[10] Hyperfluorescence of some defects of the retinal pigment epithelium is demonstrated in Figure 1. Late hyperfluorescence was therefore graded as diffuse leakage of indocyanine green only if changes in the retinal pigment epithelium could not be found biomicroscopically or during fluorescein angiography. Thus, we believe the hyperfluorescence is caused by a hyperpermeability of choroidal vessels in this area. These cases could indicate that the focal hyperfluorescent spot represents the most active site of a disease that seems to affect a larger portion of the choroid. These cases also demonstrate that significant exudation of indocyanine green cannot be a physiologic phenomenon because such differences between exuding and nonexuding areas should otherwise not be visible.

Perfusion deficits could be detected with in-

docyanine green in 12 of our patients (63%) and with fluorescein in two (11%). The reason for this difference is that the visibility with fluorescein centrally is impaired by the foveal xanthophyll and the rapid exudation of fluorescein that prevents a detection of small focal delays. No conclusion can be drawn about whether or not this delayed choroidal filling is of primary or secondary nature. It is therefore not possible to learn whether the primary cause of central serous chorioretinopathy is inflammatory or ischemic.

Newer concepts of the pathogenesis of central serous chorioretinopathy always must deal with the observation that a focal destruction of the retinal pigment epithelium alone would not cause a serous retinal detachment. It is well known from laser coagulation burns that reabsorption of serous fluid is accelerated.[20] Spitznas[6] proposed that a focal area of pigment epithelial cells, resulting from the malfunction of some ion pumps, leads to a fluid movement in the wrong direction. Marmor[7] hypothesized that a focal dysfunction cannot cause a serous bleb because surrounding cells would always compensate for this deficit. Therefore, a general dysfunction of the retinal pigment epithelium was suggested as the underlying cause of central serous chorioretinopathy.

From our observations with indocyanine green we propose that central serous chorioretinopathy originates primarily in the choroid. We conclude from the angiograms that an area larger than the focal hyperfluorescent spot is affected by an infectious or vascular abnormality. This process has two consequences. Protein exudes into the choroidal extravascular space as indicated by indocyanine green hyperfluorescence and the function of the retinal pigment epithelium is destroyed in the center and probably impaired in the entire area. The extravascular protein concentration in the choroid is usually low,[21] which is the main reason for the high colloid osmotic pressure of its vessels. However, exudation of large amounts of protein significantly lowers this pressure gradient and reduces the suction capacity of the choroid. A larger area of impaired choroidal function would therefore explain the bleb formation in central serous chorioretinopathy. It would also explain why the area of scarring in the retinal pigment epithelium is usually greater than the original focal hyperfluorescent spot during active disease. Additionally, it might explain why laser coagulation has no permanent effect on the course of central serous chorioretinopathy,[5] because it may temporarily seal the leak in the retinal pigment epithelium but it does not affect its choroidal origin.

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OPHTHALMIC MINIATURE

Kitty was very proud of her own eyes, quite rightly, they were her finest feature. Now that we have both grown older they show not only her beauty, but the darker untouchable side of her character as well. Her skin has remained as smooth as when she was a little girl, so she thinks that age has not touched her, but it has gathered in her eyes, and the depth of her bitterness is quite frightening. I see people shy away from her gaze more and more. It hurts them. I'm afraid it is her eyes that will give her away in the end. That is where the focus of her madness lies.

Lisa St. Aubin de Terán, *Joanna*
London, Virago Press, 1990, p. 244

Fluorescein Angiography in the Diagnosis of Giant Cell Arteritis

R. Michael Siatkowski, M.D., J. Donald M. Gass, M.D., Joel S. Glaser, M.D., J. Lawton Smith, M.D., Norman J. Schatz, M.D., and Joyce Schiffman, M.S.

Clinical data and fundus fluorescein angiograms were analyzed from 35 patients with acute (onset less than four weeks) anterior ischemic optic neuropathy. Nineteen of the 35 patients (54%) had nonarteritic disease, and 16 patients (46%) had giant cell arteritis confirmed by biopsy. Patients with arteritis had higher erythrocyte sedimentation rates, larger cup/disk ratios, and delayed fluorescein dye appearance and choroidal filling times. Three additional patients with cranial arteritis confirmed by biopsy, but without visual loss, had angiographic characteristics similar to patients with arteritic ischemic neuropathy. We consider fluorescein angiography a valuable diagnostic adjunct in identifying patients with giant cell arteritis.

ANTERIOR ISCHEMIC OPTIC NEUROPATHY is a well-recognized cause of visual loss in the presenescent and elderly population. Described originally by François[1] in 1962 as pseudopapillitis vasculaires, the first English-language report appeared in 1966.[2] The largest subgroup, approximately 88%, is unrelated to underlying arteritis, but constitutes the common, or arteriosclerotic form, according to a study of 600 patients.[3] Identifying the small proportion of ischemic optic neuropathies secondary to cranial arteritis is crucial, for this condition constitutes a true ophthalmic emergency. Prompt institution of high-dose systemic corticosteroids minimizes the chance of involvement of the fellow eye, maximizes the possibility of visual recovery in the initially affected eye, and diminishes the potential of serious cardiac, neurologic, or systemic sequelae.

To assess the value of fluorescein angiography in identifying patients with giant cell arteritis, we compared the clinical and angiographic characteristics of 19 patients with cranial arteritis confirmed by biopsy (16 with ischemic optic neuropathy and three without visual loss) and 19 patients with nonarteritic ischemic optic neuropathy.

Patients and Methods

The charts of 968 patients in whom ischemic optic neuropathy was diagnosed at the Bascom Palmer Eye Institute over a 20-year period (1972 to 1992) were examined. Of these 968 patients, 98 (10%) had giant cell arteritis confirmed by biopsy, and 16 of these 98 patients (16%) underwent fluorescein angiography. The remaining 870 patients (90%) were considered to have nonarteritic ischemic optic neuropathy, and 19 (2%) of them had angiography performed. Thus, 35 of the 968 patients (4%) had fluorescein angiography performed within the acute phase, defined as the first month after the onset of visual symptoms.

Within the 35 patients studied angiographically, 16 (46%) had giant cell arteritis, confirmed by superficial temporal artery biopsies; three of the 16 (19%) had bilateral visual involvement at the time of our examination. Nonarteritic ischemic optic neuropathy was diagnosed in 19 of the 35 patients (54%) on the basis of the following characteristic criteria: abrupt unilateral visual loss, acute optic disk swelling, no symptoms of polymyalgia, and a Westergren erythrocyte sedimentation rate of 45 mm/hr or less. Temporal artery biopsies performed in two patients without systemic symptoms but with

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Reprint requests to J. S. Glaser, M.D., 900 N.W. 14th St., Miami, FL 33136.

sedimentation rates of 55 and 57 mm/hr disclosed no giant cell arteritis.

We identified three additional patients with arteritis confirmed by biopsy, but without secondary visual loss, who had undergone fluorescein angiography.

Patient age and sedimentation rate (when available) were recorded. Fundus photographs and fluorescein angiograms for each patient were reviewed in a masked manner by two of us (R.M.S., J.D.M.G.), and the following information was recorded: cup/disk ratio in the unaffected fellow eye (in unilateral cases) estimated to the nearest 0.1; the presence of pale disk edema (Fig. 1); fluorescein appearance time in the choroid and central retinal artery; the time at which all choroidal lobules were filled; time of first laminar venous flow; and the time of initial total venous filling. In almost all cases, these values were easily determined; in the event of a discrepancy, the opinion of the senior examiner (J.D.M.G.) was used.

Patients were assigned to the following three groups: those with nonarteritic ischemic optic neuropathy, those with arteritic ischemic optic neuropathy, and those with cranial arteritis without secondary visual loss. The difference in means of these clinical and angiographic factors was compared by using the Student's *t*-test. To minimize the possibility of falsely over- or under-estimating the angiographic values, we averaged the time of the photographic frame for the characteristic in question, and the time of the preceding frame. Analyses were performed by using three different variables (for example, time of first frame with dye, time of preceding frame, and the average of the two) for the previously mentioned angiographic characteristics. Confidence intervals on sensitivity and specificity proportions for selected angiographic data were determined from the cumulative binomial distribution, by using StatXact statistical software (Cutel Software Corporation, StatXact Version 2, 1991, Cambridge, Massachusetts).

Repeat angiography was performed on three patients with bilateral arteritic ischemic optic neuropathy after corticosteroid therapy for two, three, and six months, respectively. In one of these three patients, visual acuity improved from an initial value of R.E.: counting fingers and L.E.: 6/200 to 20/40 in both eyes. Visual acuity in the other two patients remained at no light perception in both eyes in one patient, and R.E.: no light perception and L.E.: 4/200 in the other patient.

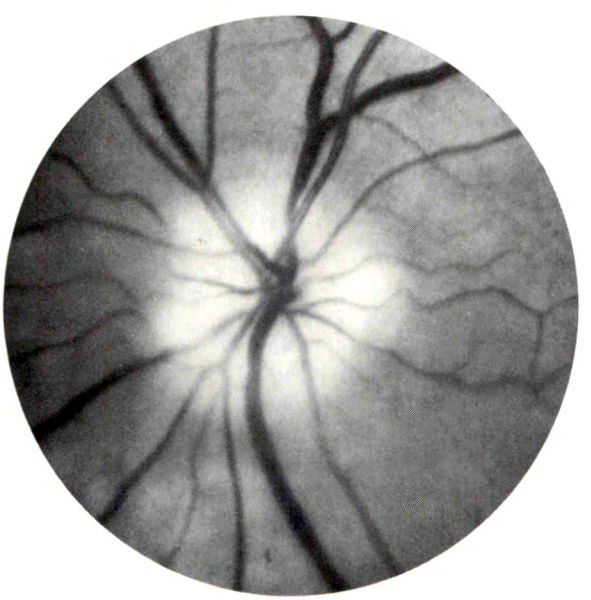


Fig. 1 (Siatkowski and associates). Milky, pale disk swelling characteristic of arteritic ischemic optic neuropathy.

Results

Characteristics of patients with nonarteritic and patients with arteritic ischemic optic neuropathy were compared (Table 1). Patients with arteritis were older (mean, 74.4 vs 67.7 years; $P = .013$), had larger cup/disk ratios (mean, 0.24 vs 0.12; $P = .012$), and higher sedimentation rates (mean, 81.9 vs 24.8 mm/hr; $P < .001$). Two patients (11%) with nonarteritic disease had sedimentation rates greater than 45 mm/hr. Three patients (19%) with arteritis had sedimentation rates less than 40 mm/hr, but one of these patients was being treated with low-dose prednisone for a respiratory problem. Omitting this case, the percentage of normal sedimentation rate in giant cell arteritis in our series was 13%.

Statistical analysis for the previously described fluorescein angiographic values showed significant differences regardless of data set used (that is, time of first frame with dye, preceding frame, or mean value). Patients with cranial arteritis had longer dye appearance times in the choroid (mean, 20.3 vs 11.29 seconds; $P < .001$) and central retinal artery (mean, 18.6 vs 11.33 seconds; $P < .001$), and had delays in laminar venous flow (mean, 23.6

TABLE 1
CLINICAL DATA OF 19 PATIENTS WITH NONARTERITIC DISEASE VS 16 PATIENTS WITH ARTERITIS

	NONARTERITIC		ARTERITIC		
	MEAN ± STANDARD DEVIATION	(RANGE)	MEAN ± STANDARD DEVIATION	(RANGE)	P VALUE
Age (yrs)	67.7 ± 7.7	(47–86)	74.4 ± 7.3	(62–88)	.013
Cup/disk ratio (fellow eye)	0.12 ± 0.08	(0.0–0.3)	0.24 ± 0.13	(0.1–0.5)	.012
Sedimentation rate (mm/hr)	24.8 ± 16.7	(4–57)	81.9 ± 36.1	(25–125)	.001
Dye appearance in the choroid (sec)	11.29 ± 2.9	(7.0–16.9)	20.3 ± 5.7	(13.4–32.6)	.001
Dye appearance in the retina (sec)	11.33 ± 2.9	(7.0–17.5)	18.6 ± 5.0	(12.8–31.3)	.001
Laminar flow (sec)	16.4 ± 3.2	(11.5–23.8)	23.6 ± 5.9	(16.3–35.0)	.001
Venous filling (sec)	21.1 ±4.2	(14.5–27.6)	29.4 ±6.4	(20.0–40.1)	.001
Choroidal filling (sec)	12.9 ± 3.1	(7.0–18.8)	29.7 ± 16.9	(14.0–86.0)	.002
Disk pallor (no. of patients)	0		10		.001

vs 16.4 seconds; $P < .001$) and total venous filling times (mean, 29.4 vs 21.1 seconds; $P < .001$). Additionally, complete choroidal filling time was delayed (mean, 29.7 vs 12.9 seconds; $P = .002$).

Of the 16 patients with arteritis, nine (56%) showed delays in choroidal perfusion time (complete choroidal filling after injection) of greater than 5.5 seconds, which is the average normal value as calculated by Mack, O'Day, and Currie,[4] as opposed to none of the patients with nonarteritic disease. Ten of 16 (63%) of the patients with arteritis were believed to have diffuse pale edema of the disk, as opposed to none of the patients with nonarteritic disease ($P < .001$, Fisher's exact test).

Data from the nonarteritic ischemic optic neuropathy group were compared with results from the three patients with arteritis without visual loss (Table 2). Patients with arteritis without ischemic optic neuropathy were older (mean, 78.0 vs 67.7 years; $P < .001$), and had prolonged arm-to-choroid (mean, 19.0 vs 11.3 seconds; $P = .001$) and choroidal filling times (mean, 23.8 vs 12.9 seconds; $P < .001$). Retinal arterial and venous flow times were not compared for these groups because of inadequate fluorescein studies in the patients with arteritis without visual loss. A smaller cup/disk ratio was again found in the nonarteritic patients (mean, 0.12 vs 0.28; $P = .210$), but without statistical significance.

Patients with arteritis with and without ischemic optic neuropathy were compared (Table 3). There were no statistically significant differences in age, cup/disk ratio, arm-to-choroid time, or choroidal filling time.

The influence of therapy in three patients

TABLE 2
CLINICAL DATA OF 19 PATIENTS WITH NONARTERITIC ISCHEMIC OPTIC NEUROPATHY VS THREE PATIENTS WITH GIANT CELL ARTERITIS WITHOUT VISUAL LOSS

	NONARTERITIC		ARTERITIS WITHOUT VISUAL LOSS		
	MEAN ± STANDARD DEVIATION	(RANGE)	MEAN ± STANDARD DEVIATION	(RANGE)	P VALUE
Age (yrs)	67.7 ± 7.7	(47–86)	78.0 ± 1.0	(77–79)	<.001
Cup/disk ratio (fellow eye)	0.12 ± 0.08	(0.0–0.3)	0.28 ± 0.16	(0.1–0.4)	.210
Dye appearance in the choroid (sec)	11.3 ± 2.9	(7.0–16.9)	19.0 ± 4.8	(14.8–24.3)	.001
Choroidal filling (sec)	12.9 ± 3.1	(7.0–18.8)	23.8 ± 3.6	(19.7–26.5)	<.001

TABLE 3
CLINICAL DATA IN 16 PATIENTS WITH ARTERITIC ISCHEMIC OPTIC NEUROPATHY AND THREE PATIENTS WITH GIANT CELL ARTERITIS WITHOUT VISUAL LOSS

	VISUAL LOSS		NO VISUAL LOSS		
	MEAN ± STANDARD DEVIATION	(RANGE)	MEAN ± STANDARD DEVIATION	(RANGE)	P VALUE
Age (yrs)	74.4 ± 7.3	(62–88)	78.0 ± 1.0	(77–79)	.076
Cup/disk ratio (fellow eye)	0.24 ± 0.13	(0.1–0.5)	0.28 ± 0.16	(0.1–0.4)	.643
Dye appearance in the choroid (sec)	20.3 ± 5.7	(13.4–32.6)	19.0 ± 4.8	(14.8–24.3)	.725
Choroidal filling (sec)	29.7 ± 16.9	(14.0–86.0)	23.8 ± 3.6	(19.7–26.5)	.565

with arteritic ischemic optic neuropathy was assessed (Table 4). Fluorescein flow improved after three months of corticosteroid therapy in Patient 1. In this patient, arm-to-choroid time decreased from 20.5 to 18.7 seconds, arm-to-retina time decreased from 19.2 to 16.8 seconds, and complete choroidal filling time decreased from more than 86 seconds to 28.5 seconds. Patients 2 and 3 had no visual improvement with corticosteroid therapy, but Patient 2 showed improved choroidal filling, although dye appearance time did not improve; in Patient 3, none of the angiographic factors improved, even after several months of treatment.

Discussion

Various clinical factors are helpful in distinguishing the arteritic form of ischemic optic neuropathy, including symptoms of polymyalgia rheumatica, increased sedimentation rate or C-reactive protein,[3] and more profound visual loss. Milky, pale disk swelling occurs at the time of sudden visual loss in 50% of patients with arteritic disease,[3] but is otherwise rare. Ischemic optic neuropathy with simultaneous central retinal or cilioretinal artery occlusion seldom occurs in nonarteritic disease, but accompanying choroidal or retinal infarctions, or both, are common in arteritis.[3]

Although the diagnostic standard of arteritis is a confirming temporal artery biopsy, skip lesions may cause results of biopsy to be false-negative in at least 4% to 5% of cases.[5,6] Nor are the other clinical factors foolproof. At least 20% of patients with temporal arteritis do not develop polymyalgia,[7] the sedimentation rate may be normal in up to 12% of patients,[8] and, conversely, may be increased in healthy persons, without obvious cause.[9,10] One fourth of patients with arteritis have initial visual acuities of 20/40 or better, and almost one fifth of patients with nonarteritic ischemic optic neuropathy have initial visual acuities of counting fingers or worse.[11]

Since the work of Novotny and Alvis[12] in 1961, fluorescein angiography has become a widely available, safe, and relatively inexpensive diagnostic tool for examining many fundus disorders. In normal eyes, after intravenous injection of 5% sodium fluorescein, choroidal filling begins ten to 15 seconds later. Approximately one to two seconds after choroidal filling starts, dye first appears in the central retinal artery; this order may be reversed, however.[13] Arm-to-choroid and arm-to-retina times are generally not longer than 15 seconds, even in elderly patients who are otherwise healthy.[13] In the next seven to ten seconds after dye appears in the eye, venous laminar flow commences and progresses to total venous filling.

TABLE 4
GIANT CELL ARTERITIS BEFORE AND AFTER TREATMENT IN THREE PATIENTS

	PATIENT 1 (RECOVERY)		PATIENT 2 (NO RECOVERY)		PATIENT 3 (NO RECOVERY)	
	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
Dye appearance in the retina (sec)	19.2	16.8	13.4	16.2	31.3	33.0
Dye appearance in the choroid (sec)	20.5	18.7	15.7	17.2	33.0	35.0
Choroidal filling (sec)	> 86	28.5	25.0	22.9	35.9	37.5

Common ischemic optic neuropathy is probably caused by vascular insufficiency in the posterior ciliary and peripapillary choroidal circulation, whether it be from hypoperfusion or actual occlusion.[14] Giant cell arteritis, however, is a diffuse, multifocal vasculitis that may involve both retinal and choroidal circulations, either primarily or as a result of ophthalmic artery occlusive disease.[3] Thus, significantly prolonged arm-to-choroid and arm-to-retina times, as well as choroidal infarctions or filling defects, should be infrequent in nonarteritic ischemic optic neuropathy, but common in cranial arteritis. Hayreh[3] has noted massive choroidal nonperfusion from occluded posterior ciliary arteries, and states that this is "almost diagnostic" of arteritic disease. Mack, O'Day, and Currie[4] found significantly prolonged choroidal filling times in patients with giant cell arteritis (mean, 69 seconds), and found that choroidal perfusion time in patients with nonarteritic ischemic optic neuropathy (mean, 5.5 seconds) is similar to that in normal individuals (mean, 5.8 seconds; $P > .990$). Additionally, Bosley and associates[15] and Bienfang[16] found significant decreases in ocular pulse amplitude in patients with arteritic ischemic optic neuropathy, which reflected ophthalmic artery involvement.

Our data were consistent with the clinical characteristics described in other studies. Patients with arteritis were older,[17] had larger cup/disk ratios,[18] and higher sedimentation rates. The percentage of patients with arteritis with normal sedimentation rates (13%) is similar to that in Cullen's earlier report.[7] None of our patients without arteritis had pale disk swelling, whereas ten of the 16 (63%) arteritic patients did, comparable to Hayreh's[3] figure of 50%.

We documented marked differences in dye appearance times between the two major forms of ischemic optic neuropathy. These angiographic values were well within normal limits (mean, 11.29 seconds) for the common ischemic optic neuropathy group, but were significantly longer in the arteritic group (mean, 20.3 seconds; $P < .001$). No eye with arteritis had dye appearance before 12.8 seconds, and no eye with nonarteritic ischemic optic neuropathy had dye appearance later than 17.5 seconds (Fig. 2). From Table 1, one can calculate that dye appeared in the choroid 1.7 seconds later, on average, than in the retina in the patients with arteritis (20.3 seconds minus 18.6 seconds), whereas in the nonarteritic group, retinal dye appearance occurred 0.04 second before choroidal appearance (11.29 seconds minus 11.33 seconds) ($P = .085$, *t*-test); although this difference is not statistically significant, it suggests preferential choroidal involvement in cranial arteritis.

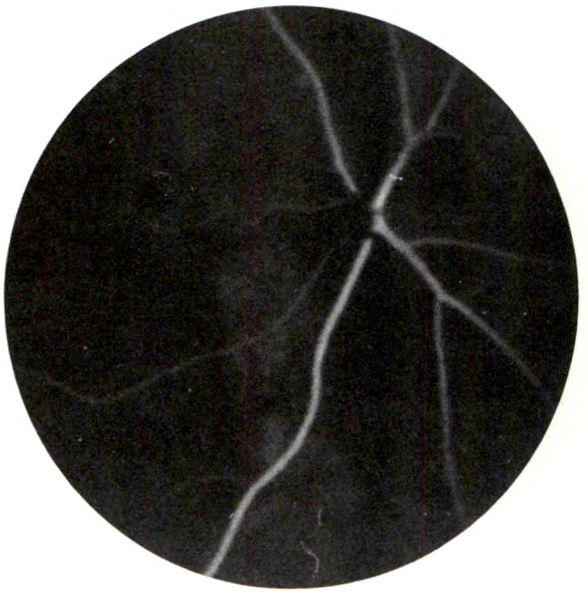


Fig. 2 (Siatkowski and associates). First appearance of fluorescein in the central retinal artery at 20.5 seconds in a patient with temporal arteritis. In patients with ischemic optic neuropathy, the dye appeared at a normal time (mean, 11.29 seconds).

Choroidal filling in nonarteritic disease was complete within a few seconds after dye was present in the central retinal artery (mean time from injection to choroidal filling, 12.9 seconds), but in cranial arteritis, there was a marked delay (mean time, 29.7 seconds; $P = .002$) (Fig. 3). Venous laminar flow and total venous filling times were significantly different in the two forms of ischemic optic neuropathy as a result of retinal arterialtransit deficits in the arteritic group, but the venous circulation itself was not as dramatically affected. Again, calculating from Table 1, the mean time from laminar flow to total venous filling was five seconds in nonarteritic disease (21.1 seconds minus 16.4 seconds), and six seconds in arteritis (29.4 seconds minus 23.6 seconds) ($P = .51$, *t*-test).

Interestingly, the three patients with giant cell arteritis, but without visual loss, had angiographic findings similar to patients with arteritic ischemic optic neuropathy. There was no difference between these two groups with re-

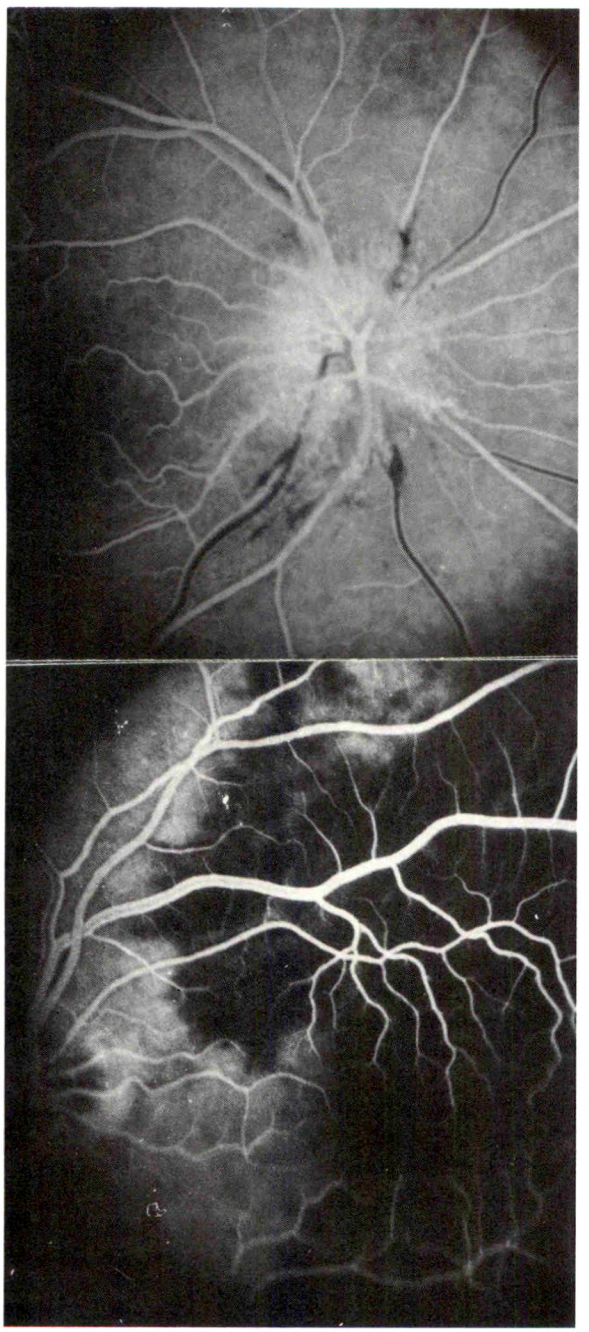


Fig. 3 (Siatkowski and associates). Top, Laminar flow and normal choroidal filling at 16.2 seconds in a patient with nonarteritic disease. Bottom, Marked choroidal nonperfusion at 32.4 seconds in a patient with arteritis.

gard to age, cup/disk ratio, and choroidal dye appearance and filling times. When compared to patients with nonarteritic optic neuropathy, these patients with arteritis were older and had prolonged arm-to-choroid and choroidal filling times. These findings may constitute evidence of deficient choroidal vascular supply in giant cell arteritis, even in the presence of normal optic nerve function. Conclusions should be drawn carefully from such a small sample size; however, the significant differences that we found should provoke further investigation.

The arteritic patient who had visual improvement with corticosteroids also had improved arm-to-retina, arm-to-choroid, and choroidal filling times (Table 4). Hayreh[3] would argue that this flow recovery does not reflect the effect of corticosteroid therapy, but that, with time, collateral choroidal circulation develops, and permits normal choroidal filling. We document, however, that the angiographic characteristics of the two patients who did not respond to therapy are either unimproved or only partially improved months after the visual loss (assuming little or no intraperson variability). Bienfang[16] found that decreased ocular pulse amplitude in patients with giant cell arteritis may never become normal in some cases. We hypothesize that corticosteroid treatment may have had a role for improved ocular blood flow and visual recovery in our case.

The sensitivity and specificity of fluorescein angiography in the diagnosis of our cases were studied (Table 5). The flow variables overlap between the two groups; for example, the longest arm-to-choroid time in the nonarteritic group is longer than the shortest time in the arteritic group. If 18 seconds is defined as the maximum normal time for choroidal filling, 93% of arteritic cases in our sample would be identified, and 94% of nonarteritic cases would be correctly eliminated. When applied to the general population, however, the percentage of cranial arteritis diagnosed could be as low as 69%, and as few as 72% of nonarteritic cases might be eliminated. Possible explanations for these low confidence intervals include the degree of severity of occlusive disease, the range of normal fluorescein patterns, and our relatively small sample size. Also, our definition of acute phase included patients with angiography performed between two and four weeks after the visual loss (five of 16 patients with arteritic optic neuropathy, and six of 19 patients with nonarteritic disease). Moreover, if pathologic flow characteristics in some cases of cranial arteritis can become normal within two weeks after a visual loss, then, if anything, the magnitude of the difference in the angiographic characteristics between these two groups is underestimated.

The carotid artery flow was not precisely assessed in our patients, and high-grade carot-

TABLE 5
SENSITIVITY AND SPECIFICITY OF SELECTED ANGIOGRAPHIC FACTORS

FACTOR	SENSITIVITY (%) (95% CONFIDENCE)	SPECIFICITY (%) (95% CONFIDENCE)
Normal time for choroidal filling (sec)		
< 14	100 (82%–100%)	71 (46%–89%)
< 15	93 (69%–100%)	71 (46%–89%)
< 16	93 (69%–100%)	82 (58%–96%)
< 17	93 (69%–100%)	88 (65%–98%)
< 18	93 (69%–100%)	94 (72%–100%)
< 19	87 (61%–98%)	100 (84%–100%)
Normal time for dye appearance in the retina (sec)		
< 12	100 (82%–100%)	53 (29%–76%)
< 13	93 (69%–100%)	71 (46%–89%)
< 14	93 (69%–100%)	82 (58%–96%)
< 15	80 (53%–95%)	94 (72%–100%)
< 16	73 (47%–92%)	94 (72%–100%)
< 17	47 (23%–72%)	100 (84%–100%)

id occlusive disease could produce angiographic characteristics similar to those found in cranial arteritis. However, none of our 35 patients had neurologic signs or symptoms, or other evidence of carotid occlusive disease.

We found fundus fluorescein angiography to be a helpful clinical tool in differentiating arteritic from nonarteritic ischemic optic neuropathy. On the basis of our data, in patients with ischemic optic neuropathy and no dye appearance by 15 seconds, or without full choroidal filling by 18 seconds, cranial arteritis should be strongly considered (assuming normal cardiovascular and carotid status). However, the limitations of our retrospective study do not enable us to verify our hypotheses. The confidence limits of our data (Table 5) are wide because of the small sample size. The possibility of a selection bias in choosing which patients in this retrospective series underwent angiography also emphasizes the need for a larger prospective series. Finally, on the basis of our three cases, further study is necessary to determine the specificity and sensitivity of fluorescein angiography in identifying giant cell arteritis in patients without visual loss. Nevertheless, in instances in which the clinical characteristics are atypical, the sedimentation rate is normal, or the results of the arterial biopsy are negative, timed rapid-sequence fluorescein angiography may lend credence to the clinical diagnosis of giant cell arteritis and justify the use of high-dose corticosteroid therapy to minimize the possibility of catastrophic visual loss.

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Retinal Vasoconstriction After Laser Treatment for Diabetic Macular Edema

María Soffía Gottfredsdóttir, M.D., Einar Stefánsson, M.D., Fridbert Jónasson, M.D., and Ingimundur Gíslason, M.D.

The diameter of retinal arterioles, venules, and their macular branches was measured before and after macular laser photocoagulation in one eye each of six men and eight women with diabetic macular edema. The macular arteriolar branches constricted 20.2% ($P < .001$) and the venular branches constricted 13.8% ($P < .001$). This autoregulatory vasoconstriction results from the improved retinal oxygenation caused by the laser treatment. By extrapolating the principles of tissue edema formation in general, we hypothesized how macular laser treatment affects diabetic macular edema. Starling's law predicts that (laser-induced) vasoconstriction and reduced intravascular hydrostatic pressure should reduce edema formation in any tissue, including the retina.

MACULAR PHOTOCOAGULATION is a proven treatment for diabetic macular edema.[1] While the effectiveness of this treatment is clinically proven, the mechanism through which the laser treatment affects the edema remains in question. One hypothesis[2] links this mechanism with the effect retinal photocoagulation has on retinal oxygen tension and vascular caliber, and the relationship between hemodynamics and tissue edema formation described in Starling's law. Starling's law gives a general description of tissue edema formation on the basis of the balance of oncotic and hydrostatic pressure differences between the intravascular compartment and the interstitial matter. Starling's law[3] states that under normal conditions, an equilibrium exists at the capillary network, in which the amount of fluid filtering outward through the arterial capillaries equals the fluid returned to the circulation by reabsorption at the venous end of the capillaries. Starling's law predicts that increased intravascular hydrostatic pressure will lead to tissue edema formation, if the oncotic pressure stays equal. Conversely, reduced intravascular pressure should reduce edema formation. Thus, treatment that reduces intravascular pressure in retinal vessels should reduce edema formation.

We postulate that macular grid photocoagulation improves the oxygenation of the retina,[4,5] leading to autoregulatory vasoconstriction, as has been shown with panretinal photocoagulation.[6] The autoregulatory vasoconstriction leads to reduced intravascular pressure in the capillary network and reduces retinal edema formation in accordance with Starling's law. We undertook this study to determine whether macular vessel constriction was associated with macular grid photocoagulation treatment for diabetic macular edema.

Material and Methods

We studied color fundus photographs of 14 eyes taken before and after grid argon laser photocoagulation of the macular area. The eyes were selected from patients who came to our diabetic eye clinic from 1985 to 1991 with diabetic macular edema, and who met the following criteria:

1. The patients had diabetic macular edema diagnosed according to the criteria of the Early Treatment Diabetic Retinopathy Study.[1] The edema was confirmed by fluorescein angiography.
2. Color fundus photographs were taken be-

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From the Department of Ophthalmology, University of Iceland, Landakotsspítali, Reykjavík, Iceland. This study was presented in part at the annual meeting of the Association for Research in Vision and Ophthalmology in Sarasota, Florida, May 4, 1992.

Reprint requests to Einar Stefánsson, University of Iceland, Landakotsspítali, 101 Reykjavík, Iceland.

fore and after argon laser photocoagulation and were of sufficient quality to measure vessel diameter. Five of the baseline photographs were taken the same day and just before the laser treatment, and most of the photographs had been taken less than one month before laser treatment. The period between baseline photography and laser treatment ranged from zero to 40 weeks (median, one week). We used baseline photographs taken the shortest time before laser treatment, and follow-up photographs taken the earliest time after laser treatment. The follow-up photographs were taken six to 118 weeks after laser treatment (median, 20 weeks).

3. The patients had undergone no previous photocoagulation.

Diabetic macular edema was diagnosed in 48 patients, and 14 patients met all the criteria. In the patients who had diabetic macular edema in both eyes, we included only the right eye in the study. The patients were six men and eight women, whose ages ranged from 40 to 85 years. Four patients used insulin and ten used oral hypoglycemic agents. The duration of diabetes mellitus varied from four to 45 years. A blue-green or green argon laser was used for scatter laser treatment of the superior, inferior, and temporal portions of the macula. One hundred thirteen to 323 spots were applied with an approximate power setting of 0.2 W and an exposure time of 0.2 second.

We measured the width of retinal vessel images on color fundus photographs with projection micrometry.[7] All the photographs were taken on 35-mm film with the same fundus camera with identical settings and development procedures. The same ophthalmologist took each patient's photographs before and after laser treatment.

The superotemporal and inferotemporal arterioles and venules were measured 1 disk diameter from the optic disk, and the macular branches of the superotemporal and inferotemporal arterioles and venules were measured 1.5 to 2 disk diameters lateral to the optic disk. The superotemporal branches were measured 1 to 1.5 disk diameters above the superior end of the optic disk and the inferotemporal branches were measured 1.5 to 2 disk diameters below the lower edge of the optic disk.

Photographs were projected onto a flat white screen and the projection apparatus was adjusted to conceal photocoagulated areas as much as possible. The distance from the projector to the screen was maintained. Vessel diameters were then measured in millimeters by two independent investigators masked to the identity of the photographs. The horizontal diameter of the optic disk was measured and divided into the vascular caliber measurement to correct for any difference in magnification between the pretreatment and posttreatment photographs. Measurement of retinal vessel diameter with projection micrometry has been compared to other methods, including microdensitometry, and was found to be a reproducible and reliable technique.[6,7]

Results

The Table shows the vessel diameter after laser treatment as a ratio of the diameter before laser treatment in the superotemporal and inferotemporal arterioles and venules and their branches. After laser treatment, a significant constriction of the macular branches of superotemporal arterioles and venules was observed. The ratio of vessel diameter after treatment to the pretreatment diameter for arteriolar branches was 0.798 ($P < .001$) and 0.862 for venular branches ($P < .001$). Similar constriction was observed in the inferotemporal branches. A significant constriction of arterioles was also observed. The ratio of vessel diameter after treatment to the pretreatment diameter was 0.946 ($P = .028$) in the superotemporal arterioles. The superotemporal venu-

TABLE
RETINAL VESSEL DIAMETER AFTER MACULAR GRID PHOTOCOAGULATION AS A RATIO OF THE DIAMETER BEFORE LASER TREATMENT

	MEAN	STANDARD DEVIATION	P VALUE*
Superotemporal arteriole	0.946	0.086	.028
Inferotemporal arteriole	0.934	0.069	.031
Superotemporal arteriolar branch	0.798	0.135	.001
Inferotemporal arteriolar branch	0.829	0.099	.001
Superotemporal venule	0.962	0.110	.235
Inferotemporal venule	0.957	0.060	.017
Superotemporal venular branch	0.862	0.092	.001
Inferotemporal venular branch	0.879	0.053	.001

*Student's *t*-test.

lar constriction was only 0.962 and was not significant (P = .235). Similar constriction was observed in the inferotemporal vessels.

Discussion

A significant constriction of superotemporal and inferotemporal arteriolar and venular branches was observed after macular grid photocoagulation for diabetic macular edema. These vessels serve the macular region, where laser photocoagulation was applied.

Oxygen has a major role in retinal autoregulation. Arterioles dilate when oxygen tension decreases or the need for oxygen increases. According to Poiseuille's law ($\Delta p = V^*8KL/\Delta r^4$, where Δp is the pressure decrease in the resistance vessels [arterioles], V is the blood flow velocity, K is a fluid constant, L is the length of resistance vessels, and r is the radius of the vessel), vasodilatation of arterioles reduces the pressure decrease in the arterioles and increases the capillary hydrostatic pressure. Similarly, increased oxygen supply after laser treatment should lead to arteriolar constriction, increased pressure decrease in the arterioles, and reduced hydrostatic pressure in the capillary network. Starling's law postulates that decreased hydrostatic capillary pressure counteracts edema formation. According to Laplace's law, there is a correlation between the hydrostatic pressure in capillaries and venules and the vascular diameter ($T = \Delta p^*r/e$, where T is the wall tension of the vessel, Δp is the transmural pressure difference, r is the vessel radius, and e is the wall thickness). High intravascular pressure is associated with dilated vessels and reduction in intravascular pressure leads to vasoconstriction. After laser treatment, the autoregulatory constriction of the resistance vessels (arterioles) leads to decreased intravascular pressure in the capillaries and venules. Our measurements confirm the constriction of both the arteriolar branches, as well as the passive venular branches.

We propose that macular grid photocoagulation works through the following mechanism. Retinal laser treatment leads to an increased oxygen flux from choroid to inner retina.[4,5] The increased oxygen supply causes an autoregulatory constriction of resistance vessels (arterioles), which leads to a reduced intravascular and transmural hydrostatic pressure in the capillaries and venules in accordance with Poiseuille's law. The decreased intravascular pressure in the capillaries and venules results in the smaller diameter of capillaries and venules according to Laplace's law. At the same time, the decreased intravascular pressure leads to reduced edema formation in accordance with Starling's law. We observed both these consequences of the laser treatment. Our measurements demonstrate the reduced vessel diameters after laser treatment. Earlier researchers[1] documented the reduced macular edema that follows macular grid photocoagulation, and we confirmed this in our patients by observing reduced thickness of the retina, improved vision, and reduced fluorescein leakage in some cases after macular laser treatment.

The reduced vascular diameter that follows macular laser treatment is in accordance with earlier studies of reduced vessel diameters and decreased blood flow after panretinal photocoagulation for proliferative diabetic retinopathy.[6,8]

The documentation of vasodilatation and increased retinal blood flow in patients with diabetic macular edema[9] also fits well with our hypothesis.

Our findings also fit well with those of an experimental study[10] that demonstrated reduced capillary diameter in a cross-sectional area in primate retina on which macular grid photocoagulation had been performed. Those authors also concluded that narrowing of the retinal capillaries may explain the resolution of macular edema.

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OPHTHALMIC MINIATURE

Puncture [kolot'e] was used as the very last resort if a patient was in critical condition. Moreover, this remedy of puncturing was also used in very many other diseases. For example for eye pain they pierced the skin between the eyes, lifting it from the bone, or at the temples or nape of the neck and so forth. To sum up in one word, there is almost no place on the human body, except for the eyes themselves, which they would not puncture in a condition of illness. I knew an Aleut who was punctured more than 40 times in different places [of the body].

Ivan Veniaminov, *Notes on the Islands of the Unalashka District*, Trans. by Lydia T. Black and R. H. Geoghegan. Kinston, Ontario, Limestone Press, 1984, pp. 290–293.

Early Revision in the Office for Adults After Unsatisfactory Blepharoptosis Correction

Richard K. Dortzbach, M.D., and Jan W. Kronish, M.D.

The most common complications of levator palpebrae superioris muscle blepharoptosis repair are undercorrection, overcorrection, and abnormalities of the eyelid contour. Previously described nonsurgical as well as surgical methods delay the repair of such complications and introduce the same confounding factors that can affect judgment of the eyelid level as during the initial surgical procedure. Twenty-two patients underwent a highly predictable surgical technique to revise unsatisfactory postoperative eyelid positions. Twenty-five of 26 eyelids (96%) had a satisfactory result and only one of 26 (4%) remained undercorrected. The revision is performed three to four days after the initial blepharoptosis correction and involves blunt separation of the wound without local anesthesia. The levator aponeurosis is advanced or recessed and resutured to the tarsus to achieve the proper eyelid height and contour. The advantages of this revision technique are as follows: (1) the procedure can be quickly and easily performed in the office; (2) the anatomic defects are corrected; (3) sharp dissection, bleeding, and edema are avoided; (4) the technique is painless and usually requires no local anesthetic injections; (5) the tone and function of the levator palpebrae superioris muscle, Müller's, and orbicularis oculi muscles remain undisturbed intraoperatively; and (6) early correction is achieved, thereby enhancing patient acceptance.

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From the Department of Ophthalmology, University of Wisconsin School of Medicine, Madison, Wisconsin (Dr. Dortzbach); and the Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami School of Medicine, Miami, Florida (Dr. Kronish).

Reprint requests to Richard K. Dortzbach, M.D., Department of Ophthalmology, University of Wisconsin Hospital and Clinics F4/334, 600 Highland Ave., Madison, WI 53792.

DESPITE CURRENT TECHNIQUES, it is difficult to predict the final result in adults who undergo blepharoptosis correction. Levator aponeurotic surgery corrects the underlying anatomic defect without disturbing other eyelid structures and, therefore, has become one of the most widely accepted repair procedures for adults with acquired blepharoptosis. Levator palpebrae superioris muscle resections may be necessary in some adults with congenital blepharoptosis who have never undergone surgical repair. Surgeons use certain guidelines preoperatively and in the operating room to determine the appropriate level at which to place the eyelid to achieve the appropriate amount of blepharoptosis correction.[1-11] However, there are many variables in adult blepharoptosis correction performed after application of local anesthetic that make it difficult to achieve consistent results.[12] This constellation of unpredictable factors frequently can lead to undercorrection, overcorrection, or contour deformities.

We devised a method of revising such unsatisfactory eyelids that is highly accurate and relatively easy to perform in the office early in the postoperative course. The accuracy of this technique is enhanced because most of the variables present during the primary blepharoptosis procedure in the operating room are either negated or minimized.

Material and Methods

The charts of all adult cases of levator palpebrae superioris muscle surgery that required early postoperative revision performed by us between January 1988 and August 1990 were reviewed. Only patients with acquired levator aponeurosis dehiscence or congenital blepharoptosis corrected in adulthood were included. Patients with myopathic, neurologic, or mechanical blepharoptosis were excluded. Initial

patient assessment included a routine ophthalmic examination and an extensive blepharoptosis evaluation. Preoperative and postoperative eyelid levels were determined by measuring the margin reflex distance to within the nearest 0.5 mm. Eyelid contours were determined by clinical observation and comparison with photographs.

The 26 eyelids of 22 patients included in this review were revised for unsatisfactory eyelid levels or contours. The eyelid position was considered unsatisfactory if there was greater than 1 mm difference of the margin reflex distance between the operated-on and unoperated-on eyelid in unilateral cases. In bilateral cases, a margin reflex distance of greater than 5 mm or less than 3 mm of either eyelid or greater than 1 mm of asymmetry between the two operated-on eyelids was judged unsatisfactory. The eyelid contour was revised if a nasal or temporal peak or marked contour asymmetry resulted. These cases were divided into the following two groups: (1) group 1, those eyelids revised for an overcorrection or undercorrection after primary blepharoptosis correction, and (2) group 2, eyelids with a contour abnormality in which the upper eyelid level was considered within 1 mm of the desired final position.

The primary blepharoptosis operation was performed in a standard manner as previously described[2,11] with certain technical modifications that influence the revision procedure. Lidocaine HCl (1%) with epinephrine 1:100,000 was used for local anesthesia in all operations. A minimal amount of local anesthetic, usually 1.0 ml, was injected subcutaneously along and above the upper eyelid crease. Infiltration of the local anesthetic in the pretarsal orbicularis oculi muscle was avoided. Intravenous sedation with monitored anesthesia was achieved at the beginning of the procedure during the infiltration of local anesthetic, but was minimized during the remainder of the procedure to reduce the sedative effects and enhance patient cooperation.

An upper-eyelid crease skin incision was made with scissors or a knife. Excessive folds of skin and preseptal orbicularis oculi muscle were excised when indicated as performed in a standard blepharoplasty. A monopolar electrocautery unit with a needle tip in the cutting mode was used to incise the orbicularis oculi muscle and the orbital septum, and to dissect the levator aponeurosis. The levator aponeurosis was advanced, and the dehisced or cut edge of the aponeurosis was sutured to the tarsus with three or four 6-0 blue polypropylene horizontal mattress sutures. The patient was raised to an upright position, and the eyelid height and contour were assessed. With the patient returned to a supine position, the initial sutures were adjusted until the eyelid was positioned 1 to 2 mm higher than the final desired level and the proper contour was achieved. This overcorrection allowed for the return of function of the anesthetized orbicularis oculi muscles (eyelid protractor muscles) postoperatively. Three 6-0 mild chromic catgut sutures were used to reform the upper eyelid crease by attaching the pretarsal orbicularis oculi muscle edge to the appropriate level on the anterior surface of the levator aponeurosis. Skin closure was achieved with a running 6-0 polypropylene suture.

All patients were instructed to apply iced compresses to the operated-on eyelids postoperatively for 48 hours to reduce postoperative edema and bleeding and to use antibiotic ointment three times daily. Three of the 26 patients received 6 mg of intravenous dexamethasone intraoperatively and 20 mg of oral prednisone twice a day for four days to control postoperative inflammation further. The application of warm compresses to the operated-on eyelids was recommended after the initial 48-hour postoperative period for an additional few days.

Patients were seen for the first postoperative examination three to four days later to allow time for the edema to clear. We found it most convenient to schedule this visit as the last appointment in the day so that if revision was necessary, it could be done without disrupting other office appointments. Revision of an undercorrection, overcorrection, or abnormality of eyelid contour was performed in those patients who had minimal eyelid swelling that allowed for an accurate measurement of the postoperative eyelid position. The procedure, performed with the patient in a reclining examination chair, took less than 30 minutes in most cases. The surgical instruments required included sterile cotton-tipped applicators, sharp-tipped Wescott or iris scissors, fine-toothed forceps, tying forceps, a needle holder, and the desired sutures. No sedative or infiltrative local anesthetic was used during the judgment phase of the revision procedure.

The patient was placed in a supine position, anesthetic drops were instilled in both eyes, and the upper face was prepped with clear

thimerosal solution. The periocular region was draped so that both eyes were exposed for comparison. The running 6-0 polypropylene skin suture was removed. The wound was spread apart with cotton-tipped applicators to expose the eyelid crease sutures, which were then excised. The cotton-tipped applicators were again used to open the wound further along the previous dissection planes to expose the anterior surface of the levator aponeurosis and tarsal plate. Bleeding during the separation of the wound was usually minimal and was controlled with gentle pressure; cautery was not necessary. The blue 6-0 polypropylene sutures that attached the levator aponeurosis to the tarsus were identified and removed. The levator aponeurosis was repositioned and resutured to the tarsal plate with three 6-0 polypropylene sutures to achieve the proper eyelid contour and height. In those cases in which the blepharoptosis was undercorrected, the levator aponeurosis was advanced further (Fig. 1); in those cases of an overcorrected blepharoptosis, the levator aponeurosis was recessed. An eyelid contour abnormality was corrected by changing the position of these sutures on the tarsal plate or by advancing or recessing the appropriate (nasal or temporal) portion of the aponeurosis (Fig. 2). The eyelid level was evaluated with the patient in the reclining and sitting positions and adjusted until the exact final desired position was achieved. A slight overcorrection was not the goal during this revision technique as it was for the primary surgical procedure.

Before closure of the wound, local anesthetic (1% lidocaine HCl with epinephrine 1:100,000) was injected along the wound edges if needed; most patients did not require any anesthetic infiltration because of wound hypesthesia. Eyelid crease sutures could be placed during the revision, but were not necessary in all patients. The skin was closed with a 6-0 polypropylene or 6-0 fast-absorbing catgut running suture. An antibiotic-corticosteroid combination ointment was applied to the wound and was continued three times a day for a week. Iced compresses were also used for an additional two days.

Results

Twenty-six eyelids were revised in 22 patients, all of whom were adults who ranged in

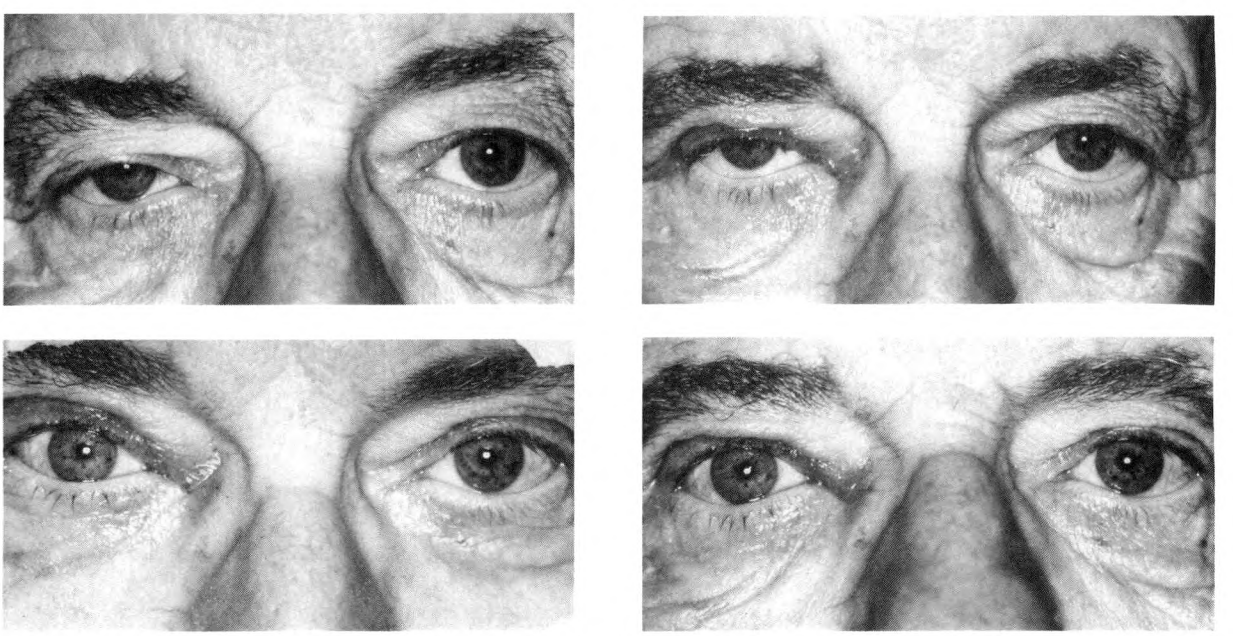


Fig. 1 (Dortzbach and Kronish). Top left, Preoperative acquired involutional blepharoptosis of the right upper eyelid in a 66-year-old man. Top right, Marked undercorrection of the right upper eyelid four days after levator palpebrae superioris muscle dehiscence repair. Bottom left, Right upper eyelid position evaluated during office revision with the patient in a supine position. Bottom right, Final right upper eyelid position with the patient in a sitting position is symmetric with the position of the contralateral upper eyelid at the conclusion of the revision.



Fig. 2 (Dortzbach and Kronish). Top left, Preoperative residual right upper eyelid blepharoptosis after multiple blepharoptosis operations in a 34-year-old woman. Top right, Moderate overcorrection with a temporal peak of the right upper eyelid four days after levator palpebrae superioris muscle dehiscence repair. Bottom left, Postrevision appearance immediately after recession of the temporal attachments of the levator aponeurosis. Bottom right, Six months after revision, the right upper eyelid position and contour remain stable.

age from 18 to 87 years (mean age, 62.3 years). Group 1 included 22 revised eyelids of 18 patients with a mean follow-up of 11.6 months (range, six to 23 months) and group 2 consisted of four patients with a mean follow-up of 7.5 months (range, six to 11 months). Prerevision data are shown in Table 1. Three of 26 eyelids had levator palpebrae superioris muscle resections for congenital blepharoptosis repaired in adulthood, and the remaining 23 eyelids had levator aponeurotic dehiscence repair or advancement for acquired blepharoptosis.

Table 2 lists the postrevision results. The data for group 1 were tabulated for revision of undercorrections alone, overcorrections alone, and undercorrections and overcorrections combined. Group 1 included more undercorrections (17 undercorrections) than overcorrections (five overcorrections). The amount of deviation from the desired final position after

TABLE 1
PREOPERATIVE DATA

	NO. OF PATIENTS	NO. OF EYELIDS	AFFECTED EYE		TYPE OF BLEPHAROPTOSIS (NO. OF EYELIDS)		PREOPERATIVE AMOUNT OF BLEPHAROPTOSIS (MM)	
			RIGHT	LEFT	CONGENITAL	ACQUIRED	MEAN (± STANDARD DEVIATION)	RANGE
Group 1*	18	22	14	8	3	19	4.4 (± 1.1)	3.0–7.0
Group 2†	4	4	1	3	0	4	3.4 (± 1.8)	2.0–7.0
Total	22	26	15	11	3	23	4.3 (± 1.2)	2.0–7.0

*Group 1 includes eyelids that required revision for an overcorrection or undercorrection after primary blepharoptosis correction.

†Group 2 includes eyelids with a contour abnormality in which the upper eyelid level was considered within 1 mm of the desired final position.

TABLE 2
POSTREVISION DATA

	NO. OF EYELIDS	AMOUNT OF DEVIATION FROM DESIRED FINAL POSITION AFTER PRIMARY BLEPHAROPTOSIS CORRECTION (MM)		AMOUNT OF REVISION (MM)		NO. OF EYELIDS (%) WITH VARYING AMOUNTS OF DEVIATION FROM DESIRED FINAL EYELID POSITION AFTER REVISION		
		MEAN (± S.D.)*	RANGE	MEAN (± S.D.)*	RANGE	0 MM	> 0–1 MM	> 1 MM
Group 1†								
Undercorrections	17	2.5 (± 0.7)	1.5–4.0	2.4 (± 0.8)	1.0–4.0	10 (58.8)	7 (41.2)	0 (0)
Overcorrections	5	2.3 (± 0.7)	2.0–3.5	2.8 (± 1.6)	1.0–4.5	2 (40)	2 (40)	1 (20)
Total	22	2.4 (± 0.7)	1.5–4.0	2.6 (± 1.2)	1.0–4.5	12 (54.6)	9 (40.9)	1 (4.5)
Group 2‡	4	N.A.	N.A.	N.A.	N.A.	2 (50)	2 (50)	0 (0)
Groups 1† and 2‡	26	N.A.	N.A.	N.A.	N.A.	14 (53.9)	11 (42.3)	1 (3.8)

*S.D. indicates standard deviation; N.A. indicates not applicable.

†Group 1 includes eyelids that required revision for an overcorrection or undercorrection after primary blepharoptosis correction.

‡Group 2 includes eyelids with a contour abnormality in which the upper eyelid level was considered within 1 mm of the desired final position.

the initial blepharoptosis operation in group 1 was 2.4 mm (range, 1.5 to 4.0 mm). These cases were revised by a mean amount of 2.6 mm (range, 1.0 to 4.5 mm). The deviation from the desired final position after revision for all of the eyelids in group 1 was within 1.0 mm for 21 of 22 eyelids (95.5%).

All four eyelids in group 2 that had revision for contour abnormalities had satisfactory final contours and eyelid levels, although two of the eyelids had final undercorrected eyelid levels of 1.0 mm or less.

We defined a satisfactory result as one in which the eyelid position achieved was within 1 mm of the desired final height with an appropriate eyelid contour. On the basis of this definition, a satisfactory result was achieved in 21 of 22 eyelids (95.5%) in group 1, all four eyelids in group 2, and 25 of 26 eyelids (96.2%) of all cases combined. The one eyelid with greater than 1 mm of deviation from the desired final position in group 1 was undercorrected by 2.5 mm; this patient did not desire further revision.

The only complication encountered after the revision procedure was a minor wound dehiscence of the skin in one patient, which was easily repaired.

Discussion

Levator aponeurotic surgery for blepharoptosis repair has advantages over alternative techniques in that the eyelid position can be adjusted with the patient's cooperation during the procedure and the normal anatomic relationships of eyelid structures are preserved. Although certain intraoperative guidelines are helpful to determine the amount of levator aponeurosis advancement or resection and the level at which to place the eyelid margin, blepharoptosis correction is still not entirely predictable. Failure rates have ranged from 5% to 39%[2,4,13,14] since the reintroduction of the surgical technique by Jones, Quickert, and Wobig[1] in 1975.

Many factors can influence the final eyelid position after blepharoptosis correction. First, anatomic and pathologic characteristics vary among patients. Intraoperative variables, as discussed by Berris,[12] can contribute to either temporary elevation or depression of the eyelid position. Factors that result in elevation of the eyelid include patient anxiety and the epinephrine contained in the local anesthetic, both of which can increase the sympathetic tone of Müller's muscle. Also, the local anesthetic reduces orbicularis oculi muscle tone, which is the protractor muscle that provides eyelid closure. When the eyelid height is judged with the patient in the supine position, it may be more elevated than when the patient is upright because of the lack of mechanical forces from the weight of a ptotic brow and dermatochalasis. Conversely, conditions that can cause deceptive depression of the eyelid level in the operating room include patient discomfort or bright overhead lights, which cause the patient to squint unconsciously. Excessive sedation may

lead to narrowing of the palpebral fissure. Paresis of the levator palpebrae superioris muscle could result from inadvertent infiltration of the local anesthetic into the anterior portion of the orbit. Further downward displacement of the eyelid may be caused by edema and hemorrhage. Finally, the contralateral upper eyelid may droop intraoperatively or postoperatively according to Hering's law of reciprocal innervation to yoke muscles after the ptotic eyelid is elevated. These inconsistencies may result in an unsatisfactory eyelid position that must be revised in the office postoperatively.

Before and during the primary blepharoptosis procedure, we take steps to decrease the influence of these variables. Preoperatively, we examine the patient for the influence of Hering's law by lifting the ptotic eyelid mechanically, as well as pharmacologically with 2.5% phenylephrine drops, and observe whether the contralateral eyelid droops when the ptotic eyelid is elevated. Intraoperatively, the patient is given either no sedative or just enough for relaxation, but overadministration of sedative is avoided to maximize cooperation. We inject only a minimal amount of local anesthetic subcutaneously and avoid infiltrating the pretarsal orbicularis oculi muscle or the deeper planes to affect the muscular function in the eyelid as little as possible. The effects of local anesthesia are further minimized when a portion of the preseptal orbicularis oculi muscle is excised with excess folds of skin at the beginning of the procedure, which is the main site of anesthetic infiltration. The monopolar electrocautery unit with the needle tip is used for all dissection once the skin has been incised, thereby greatly reducing edema and bleeding. The bright overhead operating-room lights are turned off and only general room lighting is used when we evaluate eyelid levels. Additionally, the eyelid position is usually assessed with the patient in both the supine and sitting positions. Finally, nonabsorbable sutures are used to attach the advanced edge of the levator aponeurosis to the tarsus to avoid postoperative disinsertion resulting from suture absorption.[13]

Nevertheless, the postoperative result remains unpredictable and sometimes unsatisfactory. As pointed out by Linberg, Vasquez, and Chao,[10] statistical analyses of results in various blepharoptosis series are most helpful in evaluating groups of data. Although these statistics are reasonably accurate for a group of patients, they do not necessarily hold true for any one individual. Moreover, different surgeons vary in their techniques so that guidelines and variables differ in their influence on the postoperative result. Even though a given surgeon has a routine procedure, the intraoperative variables weigh differently from case to case, thereby leading to inconsistencies. We studied how these unpredictable results can be dealt with best postoperatively.

Other authors have established successful methods of revision. Medical treatment for overcorrections may entail ocular massage and stretching of the upper eyelid[6,15] or suture removal.[6,11] Surgical management may involve levator palpebrae superioris muscle tenotomy,[6] anterior tarsectomy,[16] levator palpebrae superioris muscle recession through a posterior conjunctival approach to the eyelid,[17] levator aponeurosis recession through an anterior approach,[14,15] or the insertion of spacers.[6] For undercorrections, standard management usually has required waiting for the postoperative inflammation, edema, and hemorrhage to resolve and scar contracture to cease. If a marked residual undercorrection persists, reoperation with levator aponeurosis advancement,[14,15] levator palpebrae superioris muscle resection,[6] or internal vertical shortening[18] can be performed. Contour abnormalities can be managed with observation or removal or addition of sutures[15] or both, or surgical revision later on.[6,14,16,18] Berris[12] described the use of adjustable sutures for revising overcorrections, undercorrections, and contour deformities one to two days postoperatively.

The ideal timing of postoperative surgical revision has not been clearly established. Linberg, Vasquez, and Chao[10] found that with their technique, the eyelid level one week postoperatively accurately predicts the final result and better predicts the ultimate outcome than the intraoperative eyelid level. Therefore, they suggest that one week postoperatively is an optimal time for surgical revision. Similarly, Shore, Bergin, and Garret[14] recommend waiting five to seven days postoperatively to perform an early adjustment. Jordan and Anderson[15] state that the timing of the surgical revision is not critical. For mild to moderate overcorrections, undercorrections, and contour abnormalities, they follow conservative nonsurgical measures for two weeks. Conversely, if they identify a severe malposition in the first few days, they recommend revision at that time and usually perform the operation in a minor surgical facility.

Although the success rates of these previously described techniques of revision are compa-

rable to our series,[14,15,18] our timing and method of revision have certain advantages. The most unique aspect of our technique is the early timing of revision. We found that the best period for adjustment is three to four days postoperatively. In most cases, this has been enough time to allow the inflammation, edema, and hemorrhage to resolve from the initial surgical procedure, and yet the wound has not healed to the point at which an incision must be made for the revision. Also, at this time, the wound can still be opened with cotton-tipped applicators as opposed to requiring toothed forceps or sharp scissor dissection that could induce pain or bleeding. We found that after the fourth day, it usually is difficult to open the wound in this manner. Because there is no incision of tissues, there is no notable bleeding or increased edema, both of which could affect the evaluation of the eyelid level. Bleeding during the revision is minimal and is easily controlled with gentle pressure; we have not had to use cautery in any patients.

An additional important advantage of this timing is that no local anesthesia is required because there is no incision of tissues or pain when separating the skin and deeper tissue layers. Severing the vertically oriented upper-eyelid sensory nerve fibers during the initial surgical procedure has been proposed as the mechanism attributed to this wound hypesthesia.[19] Anxiety is reduced and motivation enhanced when patients are told that injections are usually not necessary. As a result, oral or intravenous sedatives have not been necessary to perform the revision. Also, distortion of the eyelid tissues as well as the potential of bleeding or hematoma formation, or both, are eliminated when local anesthetic is not injected. The potential effects of epinephrine in the anesthetic agent on Müller's muscle tone are avoided. Most importantly, the strength of the protractor orbicularis oculi muscle is undisturbed during the judgment part of the revision without the effects of local anesthesia. All of these factors help to maintain a more normal eyelid function and facilitate accurate evaluation of the eyelid level.

Another advantage of this method of revision is that it is easily performed in the office rather than an operating room and requires only a minor surgical setup with just a few instruments. The procedure is short, usually taking less than 30 minutes.

Although no technique of revision can offer certainty of the final result, our method was reasonably accurate in the context of our entire surgical approach to these patients. We found that in most cases, examination of patients three to four days after levator palpebrae superioris muscle surgery is an accurate time to predict whether a marked overcorrection, undercorrection, or abnormal contour will result. One contraindication to early revision would be marked postoperative edema or hemorrhage, or both, which distort the eyelid, making revision more difficult technically, and preclude accurate determination of the level at which to place the eyelid. When massive swelling is present, we defer any revision for an additional three to five days and reexamine the patient at that time. If an accurate assessment can be made at that later time, revision is performed when indicated in a similar manner; however, the patient will usually require an initial subcutaneous injection of local anesthetic. Conversely, if the swelling still has not resolved, consideration of revision is deferred until the proper evaluation can be made. Another contraindication would be an anxious patient who would not tolerate this procedure in the office without sedation. Thus far, no patient has refused our method of revision. We advocate discussing the possibility of the need for early revision with all patients before blepharoptosis correction. As Shore, Bergin, and Garret[14] observed, most patients welcome early correction of their postoperative eyelid deformity and leaving the office with the eyelid improved.

Although our series of patients included only adults, older children who undergo aponeurotic surgery or small levator palpebrae superioris muscle resections and who are cooperative should also be considered candidates for this early revision technique. More postoperative edema usually develops after moderate to large levator palpebrae superioris muscle resections in children, which makes early revision unwise. For young children who require general anesthesia for revision, we usually recommend observation of postoperative abnormalities until the eyelid heals. If gross overcorrection or contour abnormalities in children cause complications from exposure, then we revise the eyelid promptly in the operating room with the patient under general anesthesia.

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A Biometric Study of Ocular Changes During Accommodation

Patrick Joi-Tsang Shum, M.D., Liang-Shi Ko, M.D., Chak-Lau Ng, M.D., and Shun-Ling Lin, M.D.

We performed a biometric study that used A-mode ultrasonography on 106 subjects during ocular accommodation. The subjects were divided into two groups; group 1 included 76 subjects and group 2 included 30 subjects. In group 1, we measured the anterior chamber depth, lens thickness, and axial length in the right eye while the left eye, wearing corrective spectacles, focused at distances of 6 m, 33 cm, and 33 cm with an additional correction of +3.0 diopters to offset any accommodative effect. In group 2, we measured the anterior chamber depth, lens thickness, and axial length in the right eye while the left eye focused at distances of 6 m, 33 cm, and 12.5 cm. Similar to the left eyes in group 1, the left eyes in group 2 wore corrective spectacles during all procedures. During accommodation, decreased anterior chamber depth and thickening of the lens were noted in all cases. In group 1, axial length significantly increased an average of 0.06 ± 0.01 mm ($P < .0005$) while the left eye focused at a distance of 33 cm. There were no significant changes with the additional +3.0 diopters ($P < .05$). In group 2, axial length significantly increased an average of 0.05 ± 0.01 mm ($P < .0005$) when the left eye focused at a distance of 33 cm, and there was further significant elongation of 0.05 ± 0.01 mm when the left eye focused at a distance of 12.5 cm. Collectively, these results suggest that axial length increases along with changes in the lens and anterior chamber depth during ocular accommodation.

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From the Department of Ophthalmology, Cathay General Hospital (Drs. Shum, Ng, and Lin), Taipei, Taiwan, Republic of China; and the Department of Ophthalmology, National Taiwan University Hospital (Dr. Ko), Taipei, Taiwan, Republic of China.

Reprint requests to Patrick Joi-Tsang Shum, M.D., Department of Ophthalmology, Cathay General Hospital, Number 280, Section 4, Jen-ai Rd., Taipei, Taiwan, Republic of China.

Previous epidemiologic studies demonstrated a positive correlation between the degree of myopia and the amount of near work.[1-3] Anatomically, most myopia is caused by an increased axial length.[4-6] Animal experiments have also shown that excessive demand on accommodation may lead to increased axial length, which can be partially offset by treatment with atropine.[7] If myopia can be induced by prolonged near work, then the accommodative effort should result in an increased axial length. However, whether changes in axial length actually occur during accommodation is still controversial. Coleman and Weininger[8] did not detect any changes with M-mode ultrasonography. Storey and Rabie[9] demonstrated increased axial length, especially in the posterior segment, with increasing accommodation in myopic subjects. Lepper and Trier[10] found that axial length increased during accommodation in some cases, whereas it decreased or remained unchanged in others. Soriano[11] found no change in axial length during accommodation.

Nevertheless, near work and myopia seem closely related. If there is no change in axial length during accommodation, it is difficult to explain the increased axial length in myopic eyes after prolonged near work. Therefore, we investigated whether there are any changes in axial length during accommodation.

Subjects and Methods

One hundred six women who were student nurses at the Cathay General Hospital in Taipei, Taiwan, and who ranged in age from 18 to 22 years participated in this study. Visual acuity

was correctable to 20/20 in each eye of each subject, and no subject had accommodation difficulties with near work. Anisometropia was less than 1.0 diopter and refractive astigmatism was less than 1.0 diopter. Initially, we measured the corneal curvature with a Topcon RK 3000 autokeratorefractometer (Topcon Corporation, Tokyo, Japan), and the refraction with a retinoscope after the pupil had been dilated with 0.5% tropicamide and 0.5% phenylephrine hydrochloride (Santen Pharmaceutical Company, Limited, Osaka, Japan). The range of spherical equivalent refraction was +1.38 to −10.50 diopters. The intraocular pressure was then measured with a Goldmann tonometer. Corneal curvature, spherical equivalent refraction, and intraocular pressure were compared between the right and left eyes with a paired *t*-test. The biometric study was not performed at this time because of cycloplegia. We measured the anterior chamber depth, lens thickness, and axial length with a Humphrey 810 ultrasonic biometer (Humphrey Instruments/Smith-Kline Company, San Leandro, California) on a subsequent day. The frequency of the transducer was 15 MHz and the average tissue velocity was 1,555 m/sec.

The subjects were divided into two groups. Group 1 included 76 subjects who were seated upright and positioned in a chin and forehead rest. According to Fisher, Ciuffreda, and Bird,[12] monocularly and binocularly induced accommodative hysteresis effects are similar in magnitude. Hence, the left eye was used for fixation and the right eye for examination. A probe tip was aligned on the visual axis in the center of the cornea of the right eye, while the left eye focused on a 20/20 line of the Snellen chart at 6 m, with full refractive correction. We collected ten acceptable measurements, defined as a set of readings that included a standard deviation less than 0.1 mm, minimal probe compression, and maximum peaks on the ultrasonogram. Before recording the data, we ensured that the subject had a sharp image of the Snellen chart. We repeated the first procedure on the right eye while the left eye focused on the 20/20 line of a near chart at 33 cm. Then, we repeated the second procedure at 33 cm, but added +3.0 diopters to the refractive correction of the left eye to offset any accommodative effect that we designed.

Group 2 included 30 subjects on whom we duplicated the first and second procedures, but modified the third procedure by having the left eyes focus on the 20/20 line of a near chart at 12.5 cm. As with the left eyes in group 1, the left eyes in group 2 wore corrective spectacles during each examination. All procedures were completed by the same examiner within a group, but different examiners were used for groups 1 and 2. Statistical analysis of the ocular changes before and after accommodation was performed with a paired *t*-test.

Results

The mean ages were 19.6 ± 0.1 and 19.8 ± 0.2 years in group 1 and group 2, respectively. No significant differences were noted in corneal curvature, intraocular pressure, or spherical equivalent refraction between the right and left eyes (Table 1).

The anterior chamber depth decreased an average of 0.10 ± 0.01 mm and 0.12 ± 0.01 mm in group 1 and group 2, respectively; and the lens thickness increased 0.16 ± 0.01 mm in both groups when the left eye focused at a distance of 33 cm. Furthermore, there was a significant increase in axial length of 0.06 ± 0.01 mm and 0.05 ± 0.01 mm in group 1 and group 2, respectively ($P < .0005$), when the left eye focused at a distance of 33 cm, but no significant changes in the axial length were noted in group 1 when a correction of +3.0 diopters was added. However, there was a

TABLE 1
CORNEAL CURVATURE, SPHERICAL EQUIVALENT REFRACTION, AND INTRAOCULAR PRESSURE FOR EACH EYE IN GROUPS 1 AND 2*

	GROUP 1 (N = 76) (MEAN ± STANDARD ERROR OF THE MEAN)	GROUP 2 (N = 30) (MEAN ± STANDARD ERROR OF THE MEAN)
Age (yrs)	19.6 ± 0.1	19.8 ± 0.2
Corneal power (D)		
Right eye	43.84 ± 0.15	44.24 ± 0.26
Left eye	43.75 ± 0.14	44.31 ± 0.25
Spherical equivalent refraction (D)		
Right eye	−3.71 ± 0.26	−3.22 ± 0.54
Left eye	−3.69 ± 0.25	−3.18 ± 0.56
Intraocular pressure (mm Hg)		
Right eye	15.0 ± 0.3	13.8 ± 0.5
Left eye	15.5 ± 0.3	14.3 ± 0.5

*No significant differences were noted between right and left eyes.

slight increase in lens thickness of 0.02 ± 0.01 mm and a decrease in anterior chamber depth of 0.03 ± 0.01 mm at this distance.

In group 2, there was a further decrease of 0.12 ± 0.01 mm in the anterior chamber depth and an increase of 0.18 ± 0.02 mm in lens thickness when the left eye focused at a distance of 12.5 cm. The axial length increased an additional 0.05 ± 0.01 mm more than that observed for accommodation at 33 cm (Table 2).

In the analysis of linear regression, there was no correlation between the refractive error and the increase in axial length during accommodation. The coefficients of linear correlation (r) were .07 and .25 in group 1 and group 2, respectively.

Discussion

Decreased anterior chamber depth and thickening of the lens occur during accommodation.[18] However, whether the axial length increases remains controversial, as increased, decreased, and unchanged axial lengths have all been found.[8-11] In our study, we found that the axial length increased during accommodation, but the change was subtle; the length increased an average of only 0.05 to 0.06 mm during accommodation at 33 cm, and further increased 0.05 mm during accommodation at 12.5 cm. Therefore, the variability of the biometric measurement itself may be greater than the changes of axial length during accommodation by cursory examination.

In our experience, the difficulties of biometric measurements during accommodation include the accommodative convergence of the eyes and the fluctuations in accommodation. Accommodative convergence may cause the misalignment of the probe with the visual axis and induce large variations among the biometric measurements. The fluctuations in accommodation constitute a physiologic phenomenon that helps an image to be focused on the retina. The fluctuations increase in magnitude when a near object is observed or when the eye is tired.[14] These increased fluctuations in accommodation may influence the results of biometric measurements. Therefore, before recording the biometric data, we had to make sure that the subject's vision was fixated on the target. Despite the general trend of axial lengthening during accommodation in our study, there were a few cases (16 of 76 in group 1 and three of 30 in group 2) that demonstrated a shortening of axial length, similar to that found by Lepper and Trier.[10] The exact mechanism of such shortening is unknown.

In group 1, when +3.0 diopters were added to offset the accommodative effect, the decreased anterior chamber depth and thickening of the lens were attenuated, but did not recover to their original state. The decrease of the anterior chamber depth was caused by the thickening of

TABLE 2
BIOMETRIC MEASUREMENTS (MEAN ± STANDARD ERROR OF THE MEAN) OF OCULAR DIMENSIONS ON RIGHT EYES WHILE LEFT EYES FOCUSED AT DIFFERENT DISTANCES IN GROUPS 1 AND 2

	GROUP 1 (N = 76)	GROUP 2 (N = 30)
Anterior chamber depth (mm)		
(1) Focus at 6 m	3.67 ± 0.03	3.70 ± 0.05
(2) Focus at 33 cm	3.58 ± 0.03	3.58 ± 0.05
(3) Focus at 33 cm with +3 D of correction	3.65 ± 0.03	—
(4) Focus at 12.5 cm	—	3.46 ± 0.05
Difference between (2) and (1)	−0.10 ± 0.01*	−0.12 ± 0.01*
Difference between (3) and (1)	−0.03 ± 0.01†	—
Difference between (4) and (2)	—	−0.12 ± 0.01*
Lens thickness (mm)		
(1) Focus at 6 m	3.49 ± 0.02	3.54 ± 0.03
(2) Focus at 33 cm	3.65 ± 0.02	3.70 ± 0.03
(3) Focus at 33 cm with +3 D of correction	3.52 ± 0.02	—
(4) Focus at 12.5 cm	—	3.88 ± 0.04
Difference between (2) and (1)	0.16 ± 0.01*	0.16 ± 0.01*
Difference between (3) and (1)	0.02 ± 0.01†	—
Difference between (4) and (2)	—	0.18 ± 0.02*
Axial length (mm)		
(1) Focus at 6 m	24.80 ± 0.12	24.43 ± 0.27
(2) Focus at 33 cm	24.86 ± 0.12	24.48 ± 0.27
(3) Focus at 33 cm with +3 D of correction	24.79 ± 0.12	—
(4) Focus at 12.5 cm	—	24.52 ± 0.27
Difference between (2) and (1)	0.06 ± 0.01*	0.05 ± 0.01*
Difference between (3) and (1)	−0.01 ± 0.01	—
Difference between (4) and (2)	—	0.05 ± 0.01*

*$P < .0005$.
†$P < .005$.

the lens, which is controlled by the parasympathetic innervation of the ciliary muscle. According to Ebenholtz,[15] the decay time of accommodative hysteresis induced by near point fixation is slow. Perhaps the long-lasting cholinergic effect may explain why there was still mild thickening of the lens despite the addition of +3.0 diopters. In our study, we did not compare the changes of vitreous length before and after accommodation because the backward movement of the posterior lens capsule may mask the changes of vitreous length in A-mode ultrasonography.

Linear regression showed no correlation between the refractive error and the increase in axial length during accommodation. Perhaps the formation or progression of myopia is related to the scleral rigidity predominantly and the prolonged accommodation is only an inducing factor in these processes. Also, the number of volunteers examined may not have been sufficient to obtain statistically significant results because the changes of axial length are subtle during accommodation.

Some authors have addressed the influence of crystalline lens thickness on the axial length in biometric measurements because sound travels faster in lens material than in aqueous and vitreous. Most ophthalmic investigators have used the standard velocities of 1,532 m/sec for the aqueous and vitreous and 1,641 m/sec for the lens. The axial length of the eye is determined by measuring the sound transmission time between each major interface of anterior chamber, lens, and vitreous chamber, and multiplying the appropriate transmission time by the velocity of sound in that tissue. Therefore, the axial length (AL) is the sum of anterior chamber depth (ACD), lens thickness (LT), and vitreous length (VL), where the vitreous length is defined to be the distance between the posterior capsule of lens and the vitreoretinal interface. The equation is:

$$AL = ACD + LT + VL.$$

In our system, the machine was designed to use the average tissue velocity of 1,555 m/sec to measure the axial length. However, we could obtain the absolute measurements (aACD, aLT, aVL, and aAL) from the measured data with the following formula[16]:

tissue thickness = velocity of sound in tissue × time.

Then, we have

$$aACD = 1{,}532 \text{ m/sec} \times ACD \div 1{,}555 \text{ m/sec}$$

$$aLT = 1{,}641 \text{ m/sec} \times LT \div 1{,}555 \text{ m/sec}$$

$$aVL = 1{,}532 \text{ m/sec} \times VL \div 1{,}555 \text{ m/sec}$$

and $aAL = aACD + aLT + aVL$.

We converted the measured data from Table 2 to the absolute measurements (Table 3). In Table 3, the lens thickness became longer and the anterior chamber depth and axial length became shorter as compared to the measurements in Table 2. However, the changes of the absolute ocular dimensions during accommo-

TABLE 3

CALCULATED ABSOLUTE MEASUREMENTS (MEAN ± STANDARD ERROR OF THE MEAN) OF OCULAR DIMENSIONS ON RIGHT EYES WHILE LEFT EYES FOCUSED AT DIFFERENT DISTANCES IN GROUPS 1 AND 2

	GROUP 1 (N = 76)	GROUP 2 (N = 30)
Absolute anterior chamber depth (mm)		
(1) Focus at 6 m	3.62 ± 0.03	3.65 ± 0.05
(2) Focus at 33 cm	3.52 ± 0.03	3.53 ± 0.05
(3) Focus at 33 cm with +3 D of correction	3.59 ± 0.03	—
(4) Focus at 12.5 cm	—	3.41 ± 0.05
Difference between (2) and (1)	−0.10 ± 0.01*	−0.12 ± 0.01*
Difference between (3) and (1)	−0.03 ± 0.01†	—
Difference between (4) and (2)	—	−0.11 ± 0.01*
Absolute lens thickness (mm)		
(1) Focus at 6 m	3.68 ± 0.02	3.74 ± 0.03
(2) Focus at 33 cm	3.85 ± 0.03	3.90 ± 0.04
(3) Focus at 33 cm with +3 D of correction	3.71 ± 0.02	—
(4) Focus at 12.5 cm	—	4.09 ± 0.04
Difference between (2) and (1)	0.17 ± 0.01*	0.17 ± 0.01*
Difference between (3) and (1)	0.02 ± 0.01†	—
Difference between (4) and (2)	—	0.19 ± 0.02*
Absolute axial length (mm)		
(1) Focus at 6 m	24.67 ± 0.12	24.31 ± 0.26
(2) Focus at 33 cm	24.74 ± 0.12	24.37 ± 0.26
(3) Focus at 33 cm with +3 D of correction	24.67 ± 0.12	—
(4) Focus at 12.5 cm	—	24.43 ± 0.26
Difference between (2) and (1)	0.07 ± 0.01*	0.06 ± 0.01*
Difference between (3) and (1)	−0.01 ± 0.01	—
Difference between (4) and (2)	—	0.06 ± 0.01*

*$P < .0005$.

†$P < .005$.

dation remained significant (Table 2). We suggest that the effect of the increased lens thickness on the biometric measurement of axial length may be compensated for by the concomitant decreased anterior chamber depth. Even if no compensation occurs, an error of 0.05 mm lengthening in the measurement of axial length will be obtained only if the lens thickness increases by 1 mm. In our studies, the increases in lens thickness during accommodation were less than an average of 0.18 mm, but the increases in axial length were about 0.05 mm. Clearly, the elongation of the axial length during accommodation could not be entirely caused by an increase in lens thickness.

Theoretically, axial length should increase during accommodation. From a mechanical viewpoint, Coleman[17] hypothesized that a pressure gradient between the compressed vitreous and the anterior chamber may occur during accommodation, which may exert stress on the sclera. Young[18] showed an increased vitreous pressure during near viewing and suggested that if it were maintained long enough, there would be a concomitant increase in the size of the vitreous chamber, which may lead to the development of axial myopia. Pathologic studies have demonstrated increased axial length and scleral thinning in myopic eyes, especially in the posterior segment.[19] By electron microscopy, an abnormal fiber bundle architecture and reduction in fibril diameter were noted in myopic sclera.[20,21] Ultrasonographic measurements of the posterior coats of the eye showed a strong inverse correlation between axial length and ocular coat thickness.[22] Such changes may have been caused by scleral stretching. The sclera is an elastic tissue in which the most extensible part is the posterior pole.[23,24] Tokoro, Funata, and Akazawa[25] also found that the sclera distended in a longitudinal direction at the equator and in both latitudinal and longitudinal directions at the posterior pole with increasing vitreous pressure.

Therefore, accommodation may conceivably induce an increase in vitreous pressure, which may cause the vitreous chamber to expand and the sclera to stretch. Because the posterior pole is the most extensible part of the sclera, it is not surprising that axial length may increase during accommodation. Increased axial length has been induced by increased intraocular pressure in animal studies[26] and an artificial myopia was induced in young rabbits by repeatedly increasing the intraocular pressure.[27,28]

In terms of ocular structure and function, the cornea and unaccommodated lens converge the light from a distant object to form an image on the retina in an emmetropic eye. When the object is moved closer to the eye, the divergence of the incident light increases. The unaccommodated emmetropic eye will converge the light from a near object to form an image behind the retina. During accommodation, the central part of the lens thickens, causing the anterior capsule to become more convex and to shift forward. These changes in the lens may not be sufficient to focus the image exactly on the retina. A small backward movement of the posterior pole may strengthen the accommodative effect. The near object may then form a clear image on the retina.

However, increased axial length during accommodation does not imply that near viewing causes myopia immediately. Scleral rigidity may contribute to the process of myopia as well as a cumulative effect. Because of structural fatigue, when a material with good elasticity is repeatedly or continuously stressed over a long period of time, it may fail to recover completely, even though the stress may be well within its elastic limits.[29] The pathogenesis of myopia is complicated, including both genetic and environmental factors. Many authors consider myopia as a multifactorial disease.[30,31] If accommodation is one of the contributing factors of myopia, axial length elongation during accommodation may explain the development or progression of myopia.

We suggest that in addition to the decrease of the anterior chamber depth and thickening of the lens, there is also an increase in axial length during accommodation.

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Three-Year Follow-up of the Fluorouracil Filtering Surgery Study

The Fluorouracil Filtering Surgery Study Group

Patients who participated in the Fluorouracil Filtering Surgery Study, a clinical trial in which patients were randomly assigned to treatment to determine the efficacy and safety of subconjunctivally injected 5-fluorouracil after filtering surgery in eyes with poor prognoses, were followed up for three years. Treatments in 49 of the 100 eyes in the 5-fluorouracil group and 73 of the 99 eyes (74%) in the standard treatment group were classified as failures, defined by reoperation for control of intraocular pressure or intraocular pressure greater than 21 mm Hg during the first three years postoperatively ($P < .001$, chi-square). Late-onset leakage of aqueous through the filtering bleb occurred more frequently in the 5-fluorouracil group (seven of 105 eyes, 7%) than in the standard treatment group (none of 108 eyes, 0%) ($P = .006$, Fisher's exact test). We recommend the use of 5-fluorouracil after trabeculectomy in eyes after previous cataract extraction or unsuccessful filtering surgery. The increased risk of late-onset conjunctival filtering bleb leaks associated with 5-fluorouracil cautions against its routine use in patients with good prognoses.

To determine the long-term safety and efficacy of postoperative subconjunctivally injected 5-fluorouracil in eyes with uncontrolled glaucoma and poor prognoses for filtering surgery (specifically, in aphakic and pseudophakic eyes and phakic eyes after failed filtering surgery), we recruited patients into a multicenter, clinical trial in which the patients were randomly assigned to treatment (the Fluorouracil Filtering Surgery Study). The baseline patient characteristics, risk factors, outcome by prospectively defined intraocular pressure levels and reoperation rates, and adverse events in the 5-fluorouracil treatment group and in the standard treatment group during the first postoperative year were previously described.[1] This study represents the three-year follow-up on these patients.

Patients and Methods

Patient recruitment began in September 1985 and follow-up for this study continued through Aug. 7, 1991. The following seven centers participated: the University of Miami, the University of Florida, the University of Illinois, Washington University, Lorain Community Hospital (Ohio), the University of Southern California, and the University of Iowa. The institutional review board at each center approved the human research study protocol before initiating recruitment. The trial was monitored by a Safety and Data Monitoring Committee.

Efforts were made to recruit all eligible patients with uncontrolled glaucoma (intraocular pressures greater than 21 mm Hg) who had undergone cataract extraction, or who had undergone at least one unsuccessful filtering procedure in a phakic eye. Specific inclusion and exclusion criteria were previously published.[1] Patients who had previously received 5-fluorouracil systemically or in the study eye were excluded. All eligible patients had uncontrolled intraocular pressures during maximally tolerated medical therapy. Only one eye of each patient was included in the study.

Postoperative studies included visual acuity determination performed by trained personnel who used a standardized refraction methodolo-

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Reprint requests to Joyce Schiffman, M.S., Statistical Coordinating Center, Bascom Palmer Eye Institute, University of Miami School of Medicine, P.O. Box 016880, Miami, FL 33101.

gy with Diabetic Retinopathy Vitrectomy Study charts under standardized illumination.[2] Intraocular pressures in eyes with normal corneal thickness were measured with certified Goldmann applanation tonometers by ophthalmologists who were masked to the treatment status. In eyes with corneal scarring or thickening, calibrated pneumatonometers and Schiötz tonometers were used. Automated computerized visual fields were performed by trained technicians by using either Octopus program 32 (Biorad, Cambridge, Massachusetts) or Humphrey 30-2 (Humphrey Instruments, San Leandro, California) with a size III stimulus.[1]

At each clinical center, either the principal ophthalmologist or an associate ophthalmologist operated on all eyes. In all cases, a trabeculectomy was performed under a limbal-based conjunctival flap. If no serious complications were noted and the conjunctival wound was watertight, patients were randomly assigned to either standard treatment (trabeculectomy without 5-fluorouracil) or to 5-fluorouracil treatment (trabeculectomy with 5-fluorouracil).

Eyes in the 5-fluorouracil treatment group received 5.0-mg (0.5-ml) injections of 5-fluorouracil solution 180 degrees from the operative site twice daily on postoperative days 1 through 7 and once daily on postoperative days 8 through 14. Eyes assigned to standard treatment received no 5-fluorouracil. Eyes in both groups received frequent topical corticosteroids and 1% atropine sulfate in the immediate postoperative period.

Patients in the standard treatment group were not given placebo injections. Intraocular pressures were measured by an ophthalmologist who was masked to treatment status at each center at six months, one year, 18 months, two years, three years, and before reoperation for intraocular pressure control in both treatment groups. Patients whose glaucoma could not be controlled underwent either reoperation with or without 5-fluorouracil, or another procedure, such as drainage seton surgery or cyclodestruction to lower intraocular pressure. The choice of procedure for reoperation was determined by the operating physician. Patients initially randomly assigned to the standard treatment group were given the option of receiving postoperative subconjunctival 5-fluorouracil injections.

Statistical analysis—Reoperation, defined as further surgery to control intraocular pressure performed within three years, and intraocular pressure greater than 21 mm Hg with or without medication at any visit on or before the three-year visit were the primary outcome events. The three-year visit interval extended from 30 to 42 months postoperatively. Variables considered as possible risk factors for filtering surgery failure included treatment and study stratum (aphakic vs phakic with previous failed filtering surgery), gender, race, ethnicity, eye color, qualifying visit intraocular pressure, qualifying visit visual acuity, age at entry into the study, number of previous ocular procedures with conjunctival incisions, time elapsed since most recent surgical procedure, location of filtering site (superior vs inferior), scarring status at surgery site, diabetes, and type of glaucoma.

These variables were analyzed univariately with chi-square tests with Yates continuity correction, *t*-tests, or Mann-Whitney tests. Continuous variables were frequently split into several clinically meaningful groups and also analyzed with chi-square tests.

Multivariate analysis of filtering surgery failure was performed with multiple logistic regression models by using backward stepwise elimination (the P value for removal of a variable was set at .1). Those variables determined to be important risk factors for failure at or before three years were also analyzed with Cox model regression where time to reoperation was the end point; this allowed the inclusion of 14 patients excluded from the three-year analysis because of loss to follow-up. Models were checked for the influence of extreme points and when appropriate, transformations of variables were used.

Results

Failure of treatment was defined as an intraocular pressure greater than 21 mm Hg with or without medication at or before the three-year postoperative visit, that is, at the one-year, 18-month, two-year, or three-year visit; or reoperation to lower intraocular pressure during the first three years postoperatively, which extended to postoperative month 42 (Table 1). Treatment was considered successful if a patient was not reoperated on before the three-year visit, and the intraocular pressure was less than or equal to 21 mm Hg at all visits. For treatment to qualify as a success, an intraocular pressure less than or equal to 21 mm Hg after the one-year visit was required. If the patient

was not examined at 18 months, two years, or three years, the three-year outcome was considered unknown. Five such patients in the 5-fluorouracil group and nine in the standard treatment group met this criterion. At three years, the failure rates were 49 of the 100 eyes followed up in the 5-fluorouracil group and 73 of the 99 eyes (74%) in the standard treatment group ($P < .001$, Mantel-Haenszel chi-square). Treatment failed in 40 of the 77 eyes (52%) with a history of cataract extraction in the 5-fluorouracil treatment group compared to 53 of the 72 eyes (74%) in the standard treatment group ($P = .0105$, chi-square). Treatment failed in nine of the 23 phakic eyes (39%) with a history of failed filtering surgery in the 5-fluorouracil treatment group vs 20 of 27 eyes (74%) in the standard treatment group ($P = .0273$, chi-square). Failure rates were also calculated on the basis of reoperation for intraocular pressure control during the first three postoperative years (Table 2). The results of these two analyses were similar.

We also used survival analysis to compare success rates between the two treatment groups (Fig. 1). The period from filtering surgery to reoperation for the purpose of lowering intraocular pressure was defined as the time to failure. At three years, the cumulative success rates were 71% (standard error = 4.9) for the 105 patients in the 5-fluorouracil treatment group and 40% (standard error = 5.3) for the 108 patients in the standard treatment group ($P < .001$, Mantel-Cox survival analysis). The three-year success rate for the eyes with a history of cataract extraction in the 5-fluorouracil treatment group was 71% (standard error = 5.6) and was 47% (standard error = 5.9) for the standard treatment group ($P < .001$, Mantel-Cox survival analysis). The three-year success rate for phakic eyes with a history of failed

TABLE 1
FAILURE RATES, WITH FAILURE DEFINED AS REOPERATION DURING FIRST THREE POSTOPERATIVE YEARS OR INTRAOCULAR PRESSURE GREATER THAN 21 MM HG WITH OR WITHOUT MEDICATION AT OR BEFORE THREE-YEAR VISIT

	5-FLUOROURACIL GROUP			STANDARD TREATMENT GROUP			
STRATUM	NO. OF EYES	NO. OF EYES IN WHICH TREATMENT FAILED	(%)	NO. OF EYES	NO. OF EYES IN WHICH TREATMENT FAILED	(%)	P VALUE*
Previous cataract extraction	77	40	(52)	72	53	(74)	.0105
Previous filtering surgery	23	9	(39)	27	20	(74)	.0273
Total	100	49	(49)	99	73	(74)	<.001†

*P = chi-square.
†Mantel-Haenszel chi-square.

TABLE 2
FAILURE RATES, WITH FAILURE DEFINED AS REOPERATION DURING FIRST THREE POSTOPERATIVE YEARS

	5-FLUOROURACIL GROUP			STANDARD TREATMENT GROUP			
STRATUM	NO. OF EYES	NO. OF EYES IN WHICH TREATMENT FAILED	(%)	NO. OF EYES	NO. OF EYES IN WHICH TREATMENT FAILED	(%)	P VALUE*
Previous cataract extraction	77	21	(27)	72	40	(56)	.001
Previous filtering surgery	23	7	(30)	27	19	(70)	.011
Total	100	28	(28)	99	59	(60)	<.001†

*P = chi-square.
†Mantel-Haenszel chi-square.

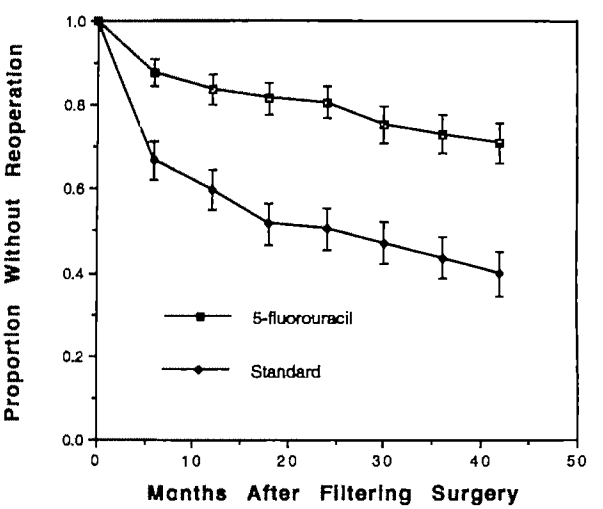


Fig. 1 (The Fluorouracil Filtering Surgery Study Group). Cumulative proportion of patients who did not undergo a reoperation for control of intraocular pressure in months after filtering surgery by treatment group (5-fluorouracil treatment group, 105 patients; standard treatment group, 108 patients). Bars indicate ± standard error.

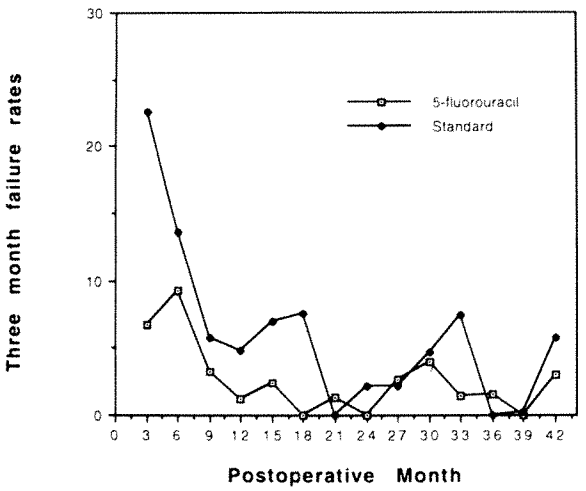


Fig. 2 (The Fluorouracil Filtering Surgery Study Group). Individual three-month reoperation rates for intraocular pressure control during the first three postoperative years by treatment group.

filtering surgery in the 5-fluorouracil treatment group was 69% (standard error = 9.8), and 27% (standard error = 9.1) for the standard treatment group (P = .007, Mantel-Cox survival analysis).

To determine if the 5-fluorouracil effect was limited to the first postoperative year or if a continued beneficial action persisted throughout the three-year follow-up, we examined estimates of the failure rates (the proportion of patients who were reoperated on) within three-month intervals. The failure rates in the two treatment groups were different within the first 18 postoperative months and were similar after 18 months (Fig. 2). The log-rank test based on the first 18 months was statistically significant (P < .001, chi-square); the test conducted on those patients in whom treatment was successful at 18 months demonstrated no statistically significant difference (P = .2, chi-square).

To determine if the use of 5-fluorouracil alone (without additional postoperative glaucoma medication) resulted in lower intraocular pressures in eyes in which surgery was successful, that is, eyes that were not reoperated on for intraocular pressure control, and in which intraocular pressures were 21 mm Hg or less, we calculated the percent of eyes in each treatment group with intraocular pressures of 15 mm Hg or less (Table 3). At three years, 67% of patients (16 of 24) in the 5-fluorouracil treatment group had intraocular pressures less than or equal to 15 mm Hg compared to 45% of patients (five of 11) in the standard treatment group (P = .283, Fisher's exact test, two-tailed). Among these patients, the mean intraocular pressure was similar in the two treatment groups (Table 4). At three years, the mean intraocular pressure was 13.2 mm Hg (standard deviation = 3.6) in the 5-fluorouracil group and 14.2 mm Hg (standard deviation = 4.7) in the standard treatment group (P = .494, *t*-test).

To determine the necessity of postoperative glaucoma medication for intraocular pressure control after successful surgery, the percent of patients in each treatment group who did not require additional medical therapy at the time of each annual visit was compared (Table 5). Of the 49 patients in the 5-fluorouracil treatment group who had controlled intraocular pressure

TABLE 3
PATIENTS WITH INTRAOCULAR PRESSURE LESS THAN OR EQUAL TO 15 MM HG*

	1 YR POSTOPERATIVE			18 MOS POSTOPERATIVE			2 YRS POSTOPERATIVE			3 YRS POSTOPERATIVE		
	NO.	(%)	P VALUE†	NO.	(%)	P VALUE†	NO.	(%)	P VALUE†	NO.	(%)	P VALUE†
5-Fluorouracil treatment	19/26	(73)	—	18/24	(75)	—	18/23	(78)	—	16/24	(67)	—
Standard treatment	8/11	(73)	>.999	8/9	(89)	.642	3/11	(27)	.008	5/11	(45)	.283
Difference		(0)			(−14)			(51)			(22)	
95% Confidence interval of difference		(−38% to 38%)			(−48% to 20%)			(13% to 89%)			(−20% to 64%)	

*Includes only those patients without reoperation and intraocular pressure ≤ 21 mm Hg and no medication for three years for control of glaucoma.

†Fisher's exact test (two tailed).

TABLE 4
MEAN INTRAOCULAR PRESSURE AMONG PATIENTS WHOSE INTRAOCULAR PRESSURE WAS LESS THAN OR EQUAL TO 21 MM HG WITHOUT REOPERATION OR MEDICATION FOR CONTROL OF GLAUCOMA

	INTRAOCULAR PRESSURE (MM HG)		
	MEAN	STANDARD DEVIATION	P VALUE*
1 yr postoperative			
5-Fluorouracil treatment (n=26)	12.2	3.6	—
Standard treatment (n=11)	13.1	4.6	.507
18 mos postoperative			
5-Fluorouracil treatment (n=24)	12.6	3.5	—
Standard treatment (n=9)	12.7	3.7	.957
2 yrs postoperative			
5-Fluorouracil treatment (n=23)	12.2	3.8	—
Standard treatment (n=11)	15.1	3.6	.037
3 yrs postoperative			
5-Fluorouracil treatment (n=24)	13.2	3.6	—
Standard treatment (n=11)	14.2	4.7	.494

*T-test.

without reoperation and who returned for the three-year visit, 31 (63%) were not taking any glaucoma medication. In the standard treatment group, 13 of 23 patients (57%) required no medical therapy (P = .773, chi-square). The percent of patients who did not require medical therapy for glaucoma control was constant during the three-year follow-up and there was no statistically significant difference with respect to treatment. However, the average number of medications required to control intraocular pressure in patients who were not reoperated on was slightly lower in the 5-fluorouracil than in the standard treatment group at two years: 0.7 medications (standard deviation = 0.9) in the 5-fluorouracil treatment group vs 1.2 medications (standard deviation = 1.1) in the standard treatment group (P = .013, *t*-test), and at three years: 0.8 medications (standard deviation = 1.0) in the 5-fluorouracil treatment group vs 1.2 medications (standard deviation = 1.2) in the standard treatment group (P = .055, *t*-test).

Visual acuity results in the 5-fluorouracil

TABLE 5
EYES WITH NO MEDICATION FOR GLAUCOMA CONTROL AT VISIT*

	5-FLUOROURACIL TREATMENT			STANDARD TREATMENT			
	NO. OF EYES	NO. OF EYES WITH NO MEDICATIONS	(%)	NO. OF EYES	NO. OF EYES WITH NO MEDICATIONS	(%)	P VALUE†
One year	51	36	(71)	25	15	(60)	.507
18 months	48	34	(71)	23	14	(61)	.570
Two years	48	28	(58)	25	12	(48)	.553
Three years	49	31	(63)	23	13	(57)	.773

*Includes only those patients without reoperation and intraocular pressure ≤ 21 mm Hg.
†Chi-square.

group were significantly worse than in the standard treatment group at one month; however, the difference in visual acuity change from the qualifying visit was not significantly different at one or two years (Table 6). At 18 months and three years, the results were significantly worse in the standard treatment group (P = .035 and .025, respectively, Mann-Whitney). The frequency distribution of the change in visual acuity (number of lines) between the preoperative and three-year visits was determined by treatment group (Fig. 3); all patients, regardless of reoperation status, were included. Visual acuity decreased to the level of no light percep-

TABLE 6
VISUAL ACUITY CHANGE AMONG ALL PATIENTS

	5-FLUOROURACIL TREATMENT MEDIAN (25 TO 75 PERCENTILE)		STANDARD TREATMENT MEDIAN (25 TO 75 PERCENTILE)		
	NO. OF PATIENTS	NO. OF LINES OF DECREASE	NO. OF PATIENTS	NO. OF LINES OF DECREASE	P VALUE*
One month	101	2 (0 to +4)	102	0 (0 to +1)	<.001
One year	98	0 (−1 to +2)	95	1 (0 to +2)	.197
18 months	92	0 (−1 to +2)	87	1 (0 to +2)	.035
Two years	92	0.5 (−1 to +3)	90	1 (0 to +3)	.075
Three years	92	1 (−1 to +3)	82	1 (0 to +4)	.025

*Mann-Whitney.

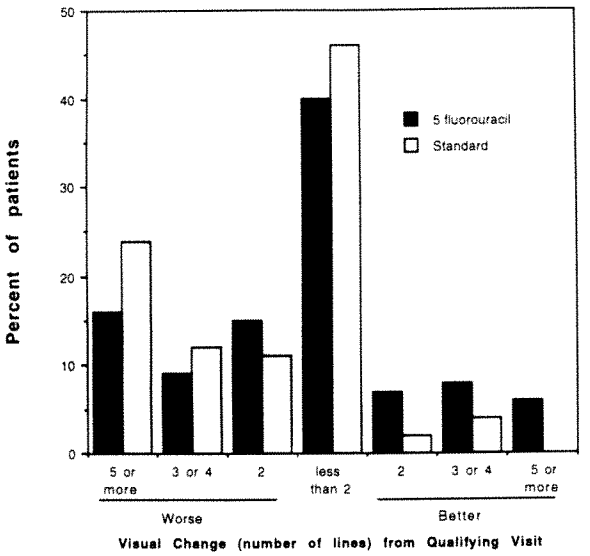


Fig. 3 (The Fluorouracil Filtering Surgery Study Group). Visual acuity change (number of lines) between the preoperative and three-year visit by treatment group.

tion in nine eyes (seven in the standard treatment group, three of which were enucleated).

Visual fields were measured at one year, 18 months, two years, and three years. Sixty-eight patients in the 5-fluorouracil group and 53 patients in the standard treatment group underwent preoperative automated visual field testing with a total visual field mean sensitivity of at least 3 dB and sufficient follow-up information to evaluate the three-year visual field status. The proportion of eyes that decreased more than 3 dB in mean sensitivity or in which visual function declined so that satisfactory automated visual field testing could not be performed was not different in the two groups (47% [32 of 68 eyes] in the 5-fluorouracil group vs 51% [27 of 53 eyes] in the standard treatment group).

Of the risk factors examined for failure by reoperation or high intraocular pressure, the following were significant in univariate analyses at a significance level of .05: (1) type of glaucoma: primary open-angle glaucoma vs secondary angle-closure glaucoma; (2) the location of the filtering site: superior vs inferior; (3) the duration of time after the last ocular surgical procedure with a conjunctival incision: six months or less vs greater than six months; and (4) the number of previous procedures with conjunctival incisions: one or two vs three or more (Table 7). Age, race, gender, stratum, Hispanic ethnicity, status of conjunctival scarring, history of ocular inflammatory disease, history of diabetes, and iris color were not statistically significant when examined with univariate analysis (Table 7).

When examined as continuous variables, preoperative intraocular pressure was statistically higher in the failure group than in the success group (35.4 mm Hg [standard deviation = 10.8] in the failure group vs 32.7 mm Hg [standard deviation = 8.0] in the success group [P = .039, *t*-test]), as was the number of previous ocular procedures with conjunctival incisions (2.2 procedures [standard deviation = 1.3] vs 1.8 procedures [standard deviation = 0.9] [P = .016, *t*-test]) (Table 8). The time (median number of days) between the study filtering surgery and the last ocular procedure with a conjunctival incision was significantly shorter in the failure group than in the success group (410 days vs 864 days, respectively) (P = .002, Mann-Whitney). The median preoperative visual acuity was also significantly lower in the failure group than in the success group (20/100 vs 20/60, respectively) (P = .025, Mann-Whitney).

Multiple logistic regression was used to evaluate the influence of risk factors for failure of filtering surgery (reoperation or intraocular pressure greater than 21 mm Hg between postoperative years 1 and 3). In addition to 5-fluorouracil, the preoperative intraocular pressure, number of previous procedures with conjunctival incisions, time elapsed from previous surgery, filtering site, iris color (brown or hazel vs blue eyes), and Hispanic ethnicity were risk factors affecting successful intraocular pressure control at three years. A survival analysis that used Cox's proportional hazard rate regression of all 213 cases in which reoperation alone was defined as an end point confirmed the statistical significance of 5-fluorouracil treatment, intraocular pressure, number of previous procedures with conjunctival incisions, elapsed time since previous ocular surgery, and Hispanic ethnicity.

Adverse effects—All hemorrhages occurred in patients with previous cataract extractions. The incidence of suprachoroidal hemorrhage was similar in the two treatment groups (five of 81 eyes in the 5-fluorouracil treatment group and five of 81 eyes in the standard treatment group). The risk of suprachoroidal hemorrhage was strongly associated with the level of preoperative intraocular pressure. None of the 63 patients with a preoperative intraocular pressure less than 30 mm Hg, three of the 47 patients

TABLE 7
RISK FACTORS AND OUTCOME

STRATUM	TOTAL NO. OF PATIENTS	PATIENTS IN WHOM TREATMENT FAILED* NO.	(%)	P VALUE†
Aphakic	149	93	(62)	—
Phakic, failed filtering procedure	50	29	(58)	.699
Race				
White	159	97	(61)	—
Black	37	22	(60)	>.999
Age (yrs)				
<50	49	29	(59)	—
≥50	150	93	(62)	.855
Conjunctival status of filtration site				
Scarred	84	50	(60)	—
Unoperated on	115	72	(63)	.769
Type of glaucoma				
Primary open-angle	66	33	(50)	—
Secondary angle-closure	35	27	(77)	.015‡
Other types	98	62	(63)	—
Ocular inflammatory disease				
History	35	24	(69)	—
No history	164	98	(60)	.435
Gender				
Male	103	64	(62)	—
Female	96	58	(60)	.918
Ethnicity				
Hispanic	27	21	(78)	—
Non-Hispanic	169	98	(58)	.081
Iris color				
Blue	56	29	(52)	—
Brown or hazel	141	91	(65)	.135
Surgical location				
Superior	127	70	(55)	—
Inferior	72	52	(72)	.026
Number of previous procedures with conjunctival incisions				
One or two	140	79	(56)	—
Three or more	59	43	(73)	.044
Time since last cutting surgery				
Six months or less	52	40	(77)	—
More than six months	146	82	(56)	.013
Diabetic status				
Diabetes (controlled by diet or oral insulin)	28	21	(75)	—
Nondiabetic	171	101	(59)	.163
Preoperative intraocular pressure (mm Hg)				
<35	109	63	(58)	—
≥35	90	59	(66)	.331
Preoperative visual acuity				
Better than 20/200	130	77	(59)	—
20/200 or worse	69	45	(65)	.501

*Reoperation or intraocular pressure over 21 mm Hg with or without medication at one year, 18 months, two years, or three years postoperatively.

†Chi-square.

‡Compares secondary angle-closure to primary open-angle glaucoma.

TABLE 8
RISK FACTORS AND OUTCOME
(CONTINUOUS VARIABLES)

	TREATMENT SUCCESSES (N = 77)		TREATMENT FAILURES (N = 122)		
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION	P VALUE
Preoperative intraocular pressure (mm Hg)	82.7	8.0	35.4	10.8	.039*
Age (yrs)	59	18	62	16	.259*
Number of previous surgeries with conjunctival incisions	1.8	0.9	2.2	1.3	.016*
Preoperative visual acuity (median)	20/60		20/100		.025†
Time since most recent ocular cutting surgery (days) (median)	864		410		.002†

*Two-sample *t*-test.
†Mann-Whitney test.

(6%) with a preoperative intraocular pressure between 30 and 39 mm Hg, four of the 36 patients (11%) with a preoperative intraocular pressure between 40 and 49 mm Hg, two of the 12 patients (17%) with a preoperative intraocular pressure between 50 and 59 mm Hg, and one of four patients (25%) with an intraocular pressure more than 60 mm Hg developed a suprachoroidal hemorrhage.[3]

Penetrating keratoplasty was performed in five eyes in the first three-year follow-up period (three eyes in the 5-fluorouracil treatment group and two in the standard treatment group). Preoperative corneal endothelial cell counts were markedly reduced in the two eyes in the standard treatment group (853 cells/mm^2 and 796 cells/mm^2). Preoperative corneal epithelial edema before the study filtering surgery precluded photography of the endothelium in two of the three eyes in the 5-fluorouracil group.

Although corneal endothelial photography was not repeated after the first postoperative year, no statistically significant difference in late-onset clinically observable corneal epithelial edema was detected between the two groups. Twenty-one percent of the patients (22 of 105) in the 5-fluorouracil group vs 13% patients (14 of 108) in the standard treatment group developed corneal epithelial edema (P = .170, chi-square).

The development of an aqueous leak in the filtering bleb characterized by a positive Seidel test was statistically more likely to occur in an eye that received 5-fluorouracil (seven of 105 [7%] vs none of 108 [0%] eyes in the standard treatment group) (P = .006, Fisher's exact test, two-tailed). The onset of leakage occurred at three, four, eight, eight, 25, 25, and 26 months after filtering surgery. Three of the seven blebs that developed a leak were located in either the inferonasal or inferotemporal quadrant, and four were positioned superiorly.

One patient in the 5-fluorouracil treatment group developed complications of endophthalmitis in an eye with an inferiorly positioned bleb that had been noted to leak chronically for six months before the development of infection. The patient had a history of a mild conjunctival discharge and injection for one week before examination for an acute decrease in visual acuity. The patient was treated with a pars plana vitrectomy and intravitreal antibiotics; visual acuity recovered to 20/30. One patient in the standard treatment group developed vitreitis and was treated for presumed bacterial endophthalmitis with pars plana vitrectomy and intravitreal antibiotics 26 months after the initial filtering procedure by an ophthalmologist who was not a study participant. No culture information was available.

Nine eyes lost the ability to perceive light during the three-year follow-up period after filtering surgery (seven eyes in the standard treatment group and two eyes in the 5-fluorouracil treatment group). Enucleation was performed for control of chronic pain or cosmetic enhancement in three of seven eyes in the standard treatment group and no eyes in the 5-fluorouracil treatment group.

Seven patients underwent cataract extraction after the study filtering surgery and before a reoperation for control of intraocular pressure (four in the 5-fluorouracil group and three in the standard treatment group). Five patients underwent cataract extraction at the same time as the first reoperation for intraocular pressure control (one in the 5-fluorouracil group and four in the standard treatment group).

Discussion

Patients with a history of cataract extraction or those who had undergone previous unsuccessful filtering surgery in a phakic eye who

received 5-fluorouracil were more likely to achieve intraocular pressure control and to avoid reoperation for at least three years. The one-year follow-up data clearly demonstrated a lower failure rate in the 5-fluorouracil–treated group than in the standard filtering surgery group.[1] This study demonstrates persistent treatment effect and that the 5-fluorouracil group continues to have a lower failure rate through the third postoperative year. However, this therapeutic maintenance most likely reflects the initial benefit of the drug rather than any new advantage occurring in late follow-up. Failure rates in the two treatment groups appear similar among patients whose filtering procedures continue to be successful 18 months postoperatively.

Although the primary end point of the study was intraocular pressure control rather than preservation of visual function, visual acuity and visual field data were collected throughout the study. The results at three years suggest that patients in the 5-fluorouracil group may lose less visual acuity than those in the standard treatment group, but further follow-up will be necessary to determine the long-term clinical importance. At one year, the visual field data were considered to be most useful as an indicator of the ocular toxic effects of 5-fluorouracil. The loss of mean sensitivity was less than 1 dB in each treatment group in those patients who had not been reoperated on and did not suggest a toxic effect related to 5-fluorouracil.[1] After three years, the proportion of eyes with a significant decrease in mean visual field sensitivity does not demonstrate a difference between the two treatment groups in patients with adequate quantitative field data at baseline and follow-up. Some patients who were unable to perform automated field testing underwent kinetic examination of the visual field. The five-year analysis will incorporate all available field data in an attempt to determine the long-term influence of 5-fluorouracil treatment and the lowering of intraocular pressure on the maintenance of visual field.

Although the use of postoperative 5-fluorouracil has been advocated to maximize the intraocular pressure–lowering effect of filtering surgery,[4,5] in this study after three years, the degree of intraocular pressure lowering among patients with controlled intraocular pressures does not appear different in the two treatment groups (Fig. 2). The proportion of eyes with low intraocular pressure (< 15 mm Hg) among eyes that did not require reoperation or glaucoma medication is not statistically different between the two groups, even though the likelihood of having successful surgery was greater in the 5-fluorouracil treatment group. Because the goal of the study was only to achieve an intraocular pressure of 21 mm Hg or less, we cannot determine the intraocular pressure–lowering maximum in either treatment group. Although this study did not demonstrate that the use of 5-fluorouracil is significantly associated with lower intraocular pressures among patients with controlled intraocular pressures, we cannot rule out this hypothesis, as shown by 95% confidence intervals (Table 3).

The beneficial effects of 5-fluorouracil on intraocular pressure control at three years must be interpreted in view of the associated adverse events. The difference in visual acuity and visual field loss between the two groups did not suggest a direct toxic effect to the retina or optic nerve. However, late-onset conjunctival bleb leaks, which may increase the risk of endophthalmitis,[6,7] were more common in the 5-fluorouracil group than in the standard treatment group. The 7% incidence of this study is less than the 25% incidence (five of 20) described in a series of young patients who underwent initial trabeculectomy with 5-fluorouracil.[7]

Certain risk factors were found in the univariate, the multiple logistic, and the Cox regression models. In all the models, the treatment was the most important variable. Other variables that were important in all the models were preoperative intraocular pressure, the number of previous ocular procedures with a conjunctival incision, and the interval between the last ocular surgery and the study filtering surgery. The five-year follow-up may clarify some other potential risk factors suggested by one or more analyses, that is, secondary angle-closure glaucoma, inferior surgical location, brown or hazel eyes, and Hispanic ethnicity.

We recommend the continued use of 5-fluorouracil in the surgical management of glaucoma in patients with a history of cataract extraction or failed filtering surgery. Although lower doses and less frequent injections of 5-fluorouracil have been found elsewhere[8,9] to promote intraocular pressure control in similar eyes, we cannot infer a long-term treatment effect of a lower-dose regimen. In view of the increased incidence of late-onset conjunctival filtering bleb leaks, we suggest caution in the use of 5-fluorouracil at the dose used in the Fluorouracil Filtering Surgery Study in eyes with good prognoses.

THE FLUOROURACIL FILTERING SURGERY STUDY INVESTIGATORS

University of Iowa Center (Iowa City, Iowa); Principal Investigator: Wallace L. M. Alward, M.D.; Coinvestigators: Thomas Farrell, M.D., Sohan Hayreh, M.D., Hansjoerg Kolder, M.D., and Benita Carney; Past Principal Investigator: Charles Phelps, M.D.†

Lorain Community Hospital (Lorain, Ohio); Principal Investigator: Michael Gressel, M.D.; Coinvestigators: John Costin, M.D., Paul Craven, M.D., and Michael Zgrabik, M.D.; Past Coinvestigators: Pamela Schremp, M.S.N., and Barbara Simashkevich.

University of Southern California Center (Los Angeles, California); Principal Investigator: Dale K. Heuer, M.D.; Coinvestigators: George Baerveldt, M.D., Don Minckler, M.D., John Irvine, M.D., Alfredo Sadun, M.D., Ronald Green, M.D., Peter McDonnell, M.D., Maryann Lloyd, M.D., Richard R. Ober, M.D., Frances Walonker, and Margaret Padilla; Past Coinvestigators: James Martone, M.D., Peter Liggett, M.D., John Lean, M.D., Eva Griffay, and Andrea Miller-Scholte.

Washington University Center (St. Louis, Missouri); Principal Investigator: Michael Kass, M.D.; Coinvestigators: Allan Kolker, M.D., Martha Farber, M.D., Lawrence Gans, M.D., Morton Smith, M.D., and Arnold Jones; Past Coinvestigators: Shirley Klenke and Alyson Owensby.

University of Miami Center (Miami, Florida); Principal Investigator: Richard K. Parrish II, M.D.; Coinvestigators: Elizabeth Hodapp, M.D., Paul F. Palmberg, M.D., Douglas R. Anderson, M.D., and Madeline Del Calvo; Past Coinvestigators: Marilyn Mule, Ann Carter, M.S., Ana Fajardo, and Yasmina Rosario.

University of Florida Center (Gainesville, Florida); Principal Investigator: Mark Sherwood, M.D.; Coinvestigators: George Stern, M.D., William Driebe, M.D., John Guy, M.D., Marwa Adi, M.D., Maher Fanous, M.D., Robert Manes, M.D., Paula Crawford, M.D., Mary Frances Smith, M.D., William Doyle, M.D., John Beneke, M.D., and Diana Shamis; Past Principal Investigator: Dale K. Heuer, M.D.; Past Coinvestigator: Harry Engel, M.D.

University of Illinois Center (Chicago, Illinois); Principal Investigator: Jacob Wilensky, M.D.; Coinvestigators: Howard Tessler, M.D., and Diane Frohlichstein; Past Coinvestigators: Robert Barnes, M.D., Eve Higginbotham, M.D., Sao Liu, M.D., Michael Shahboz, M.D., and Gary Scholes, M.D.

National Eye Institute (Bethesda, Maryland); Project Officer: Richard L. Mowery, Ph.D.; Past Project Officers: Anita Suran, Ph.D. (1985), Israel Goldberg, Ph.D. (1985 to 1986), and Peter Dudley, Ph.D. (1986 to 1988).

Statistical Coordinating Center, The University of Miami (Miami, Florida); Principal Investigator: Joyce Schiffman, M.S.; Coinvestigators: Ross Schwelm, M.S., William Feuer, M.S., Dennis Gillings, Ph.D., and Luz Gual; Past Coinvestigator: Patricia Anderson.

Safety and Data Monitoring Committee: Chairman: Curt Furberg, M.D.; Members: David Dueker, M.D., Sylvan B. Green, M.D., Alan M. Laties, M.D., Katherine E. Peres, Ph.D., and Robert F. Taylor, M.D.; Ex Officio Members: Dennis Gillings, Ph.D., Richard L. Mowery, Ph.D., Joyce Schiffman, M.S., and Richard K. Parrish II, M.D.; Past Chairman: M. Christina Leske, M.D. (1985 to 1986); Past Member: Donald Minckler, M.D. (1985 to 1986); Past Ex Officio Members: Peter Dudley, Ph.D. (1986 to 1988), and Israel Goldberg, Ph.D. (1985 to 1986).

Visual Field Reading Center, University of Missouri (Columbia, Missouri); Principal Investigator: David Dueker, M.D.

Steering Committee: Chairman: Richard K. Parrish II, M.D.; Members: Wallace L. M. Alward, M.D., Michael Gressel, M.D., Dale K. Heuer, M.D., Michael Kass, M.D., Richard L. Mowery, Ph.D., Joyce Schiffman, M.S., Mark Sherwood, M.D., and Jacob Wilensky, M.D.; Past Members: Anita Suran, Ph.D. (1985), Israel Goldberg, Ph.D. (1985 to 1986), and Peter Dudley, Ph.D. (1986 to 1988).

†Deceased.

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OPHTHALMIC MINIATURE

They say I'm not hungry, but I still feel hungry, only now it's a kind of panic hungry, and that's not the right kind. Ever watch one of your little kids try to catch a ball? He gets so excited with the idea he's going to catch it he shuts his eyes. That's me now. I walk up to the plate, having come all this way—a lot of hotels, a lot of shagging—and my eyes feel shut. And I stand up there trying to push my eyeballs through my eyelids, and my retinas register maybe a little green, and the black patch of some nuns in far left field. That's panic hungry.

John Updike, *Museums and Women*
New York, Alfred A. Knopf, 1972, pp. 166–167

Corneal Endothelial Cell Counts After Molteno Implantation

Mark L. McDermott, M.D., Ronald P. Swendris, M.D., Dong H. Shin, M.D., Mark S. Juzych, M.D., and John W. Cowden, M.D.

Implantation of a Molteno drainage shunt has been shown to be effective in advanced glaucoma. Foreign substances within the anterior chamber have been known to cause progressive endothelial cell loss. We undertook a study to evaluate the endothelial effects of an indwelling Molteno drainage shunt. Nineteen patients who underwent uneventful implantation of a Molteno drainage shunt for advanced aphakic or pseudophakic glaucoma were followed up. Serial endothelial cell counts were obtained in a masked fashion. During follow-up periods ranging from 5.4 to 25.7 months, endothelial cell loss averaged two cells per square millimeter per postoperative month with a 95% confidence interval of positive seven cells to negative ten cells per square millimeter per postoperative month. No clinically significant progressive trend in endothelial cell loss was seen in patients undergoing uncomplicated Molteno drainage procedures. Larger sample sizes with longer follow-up will be necessary to establish whether a Molteno drainage shunt causes clinically remarkable endothelial cell loss.

PLACEMENT of a drainage shunt in patients with uncontrolled glaucoma is now accepted practice.[1-3] With the increased scope of patients eligible for the implantation of such a device, the long-term safety of these devices for the corneal endothelium is not well known. The placement of a silicone tube within the anterior chamber has the potential for multiple endothelial side effects. The active reciprocation of aqueous humor through the silicone tube during the cardiac cycle may create a fluid jet that may impinge on the corneal endothelium during diastole. Additionally, the placement of the tube close to the corneal endothelium may set up a vicious cycle of intermittent corneal endothelial wounding followed by inflammation and corneal endothelial migration to cover the defect followed by rewounding. In this situation the potential exists for ongoing cell loss. The important factor in this hypothesis would be intermittent tube touch. With constant tube touch there may be scarring and fibrosis which, while initially causing a greater reduction in cell count, will result in a stable fixed tube-corneal attachment with no further cell loss. With intermittent tube touch, which can occur when the patient rubs the eye, the potential exists for repeated endothelial wounding and progressive cell loss. Additionally, intermittent tube-uveal touch may cause chronic low-grade inflammation, resulting in endothelial damage. Finally there may be foreign body inflammation secondary to the silicone tube itself. The purpose of our study, therefore, was to assess the endothelial cell counts in patients who had uneventful placement of a Molteno drainage shunt.

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From the Kresge Eye Institute, Wayne State University School of Medicine, Detroit, Michigan. This study was presented in part as a poster at the Association for Research in Vision and Ophthalmology Annual Meeting, Sarasota, Florida, May 7, 1992.

Reprint requests to Mark L. McDermott, M.D., Kresge Eye Institute, Department of Ophthalmology, Wayne State University School of Medicine, 4717 St. Antoine, Detroit, MI 48201.

Patients and Methods

Nineteen patients in whom aphakic or pseudophakic glaucoma was diagnosed were entered into the study. The patients all underwent identical Molteno drainage shunt implantation procedures by the same surgeon (D.H.S.). Briefly, this procedure consisted of preparation of a

10-mm cord length superotemporal or inferonasal fornix-based conjunctival flap including Tenon's capsule with a radial relaxation wing on one side. After blunt dissection of the flap as far posteriorly as possible, a single plate Molteno shunt was inserted into the subtenon's space with the anterior border of the plate no closer than 10 mm from the corneoscleral limbus. The length of the silicone tube was estimated and cut beveled end up at a length to permit its extension 2 to 3 mm into the anterior chamber.[4] To limit postoperative hypotony, a 9-0 nylon releasable internal ligature was tied tightly around the silicone tube 1.5 mm from its beveled end within the anterior chamber. A paracentesis track was prepared by using a 23-gauge butterfly needle 2 mm from the corneal periphery. The tube with the attached ligature was passed through the paracentesis track into the anterior chamber. Close attention was paid to ensure that the tube lay as far from the cornea as possible without touching the iris. The external portion of the tube was covered with a 5 × 7-mm scleral patch graft, which was sutured to the recipient sclera with multiple interrupted 9-0 nylon sutures. The conjunctival peritomy was closed over the site with interrupted 9-0 nylon sutures. Postoperative medications included topical corticosteroids, antibiotics, and cycloplegics. The internal ligature around the silicone tube was lysed with an argon laser (50-μm spot size, 0.1-second duration, 1.0-W power) if the intraocular pressure was judged to be clinically unacceptable.[4] During routine scheduled follow-up visits the patients underwent specular microscopy (×40 cone) of the central endothelium in the operated-on eye. Enlarged negatives were projected on a viewbox and the cells were traced and counted in a masked fashion by the same examiner (M.L.M.). For each patient a rate of cell change per month was calculated from the change in cell counts between successive visits and the elapsed time between visits. For patients examined more than two times a cell change per postoperative month was determined by the quotient of the difference in cell number between the present visit and the most recent previous visit over the elapsed time between visits. For the mean cell change per postoperative month the values determined after each visit were averaged. Although attempts were made to schedule equal intervals between microscopy, the duration between visits was primarily a function of the patient's ability to travel.

Results

Follow-up ranged from 5.4 to 25.7 months with a mean of 10.0 ± 6.7 months (mean ± standard deviation). Twelve (63%) patients underwent three or more endothelial cell counts at an average of 6.0 ± 4.4 months between counts. The Figure shows endothelial cell counts plotted as a function of time for each patient. On inspection, all curves were essentially flat, indicating a stable cell count. A mean endothelial cell loss of approximately two cells per square millimeter per postoperative month was seen for all patients. The 95% confidence interval for this cell change ranged from a positive 6.7 to a negative 10.2 cells per square millimeter per postoperative month.

Discussion

Our rate of cell loss of two cells per square millimeter per postoperative month lies between that reported for uncomplicated extracapsular cataract extraction and the age-dependent loss of endothelial cells in normal individuals who have never had ocular surgery. In a series of 101 patients undergoing uncomplicated extracapsular cataract extraction with a one-year follow-up, Bates, Hiorns, and Cheng[5] showed an average rate of cell loss of five cells per square millimeter per postoperative month. In assessing the age-related loss of endothelial cells, data from Yee and associates[6] permit an estimate of 1.3 cells per square millimeter per month of life to be calculated.

The observed interposition of our study's rate of cell loss per postoperative month between that seen in cataract extraction and that related to aging is expected because the initial surgical trauma associated with the Molteno implant placement is probably less than that associated with cataract extraction or trabeculectomy. Implantation of a Molteno device is by and large an extraocular procedure. The only intraocular portion is preparation of a paracentesis track for silicone tube placement. Postoperative complications such as flat anterior chamber, degree of inflammatory response, and tube-corneal touch will surely result in most of the cell loss. With meticulous surgical technique, appropriate safeguards against postoperative hypotony,[4] and careful postoperative follow-up, endothelial cell loss from these factors can be minimized.

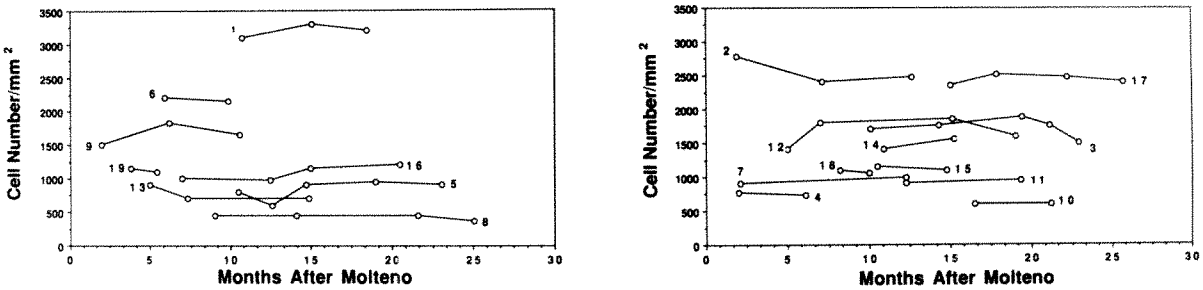


Figure (McDermott and associates). Composite plot of endothelial cell number vs months after Molteno implantation for all 19 patients. The numbers adjacent to the open circles indicate the patient numbers.

In contrast to the results described here, there have been reports suggesting a decreased survival rate of corneal grafts in eyes containing Molteno shunts.[7,8] In these eyes, however, it would be difficult to attribute endothelial cell loss to the device because most corneal transplants undergo a 60% reduction in central endothelial cell count during the first two postoperative years.[5] Consequently, it would be difficult to distinguish cell attrition caused by the Molteno device from the cell loss that occurs in the natural course after a corneal transplant. Nevertheless, it is possible that given the reduced reserve of endothelial cells in corneas after keratoplasty, even a small increase in cell attrition of the order of two cells per square millimeter per postoperative month may result in increased rates of corneal decompensation. There is also the possibility that the full-thickness trephination and grafting may alter anterior segment support, resulting in a flaccid anterior segment that would promote tube-endothelial touch and an accelerated rate of cell loss. Additionally, a flaccid anterior segment may promote or tube-uveal touch with attendant inflammation.

Besides direct trauma to the endothelium, inflammation alone may affect the endothelium. These effects include neutrophil-generated hydrolases, free radicals, and phagocytic activity. Trauma to the iris may result in generation of prostaglandins, some of which may affect endothelial sodium/potassium adenosine triphosphatase activity. One prostaglandin product, 12 R hydroxyicosatetraenoic acid, has been shown to cause corneal swelling in humans by an in vitro corneal perfusion apparatus.[9] Chronic inflammation has been shown to reduce sodium/potassium adenosine triphosphatase pump site density and increase corneal endothelial permeability in a rabbit uveitis model.[10]

Another source of inflammation can be of a foreign-body type in response to the silicone tube. A histopathologic study of the Molteno implant has shown, however, that no appreciable inflammatory reaction is induced by the Molteno plate and the silicone tube entering into the anterior chamber.[11] Furthermore, solid silicone prostheses have been thought to be well tolerated in other areas of the body. More likely, the causes of inflammation center on tube-uveal touch or endothelial wounding. Both of these causes can be minimized with proper tube placement. Nevertheless a low-grade inflammatory response may exist and this may be enough to shorten graft survival either directly via the previously mentioned mechanisms or by accelerating the afferent and efferent limbs of the immune response, resulting in graft rejection.

The range of endothelial cell change per postoperative month does include spread into a positive cell change. Since the human endothelium has little mitotic potential, the positive cell change is most likely representative of sampling differences between successive examinations, as well as variability in central endothelial counting. Sampling differences are especially important in patients with low cell counts. In those patients a maximum possible number of cells was traced and counted.[12] Nevertheless in those patients the number of cells counted was necessarily small. Possibly the sampling difference could mask a larger net cell loss in some patients. A more sensitive technique may be to perform regional specular microscopy in the area of the silicone tube. In our patients, however, the placement of the silicone tube was in the far periphery, and specular microscopy in these areas is technically difficult because of the corneal positioning to allow applanation with the specular microscope cone and the presence of peripheral cor-

neal arcus, which limits visualization of the endothelium.

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Neuro-ophthalmologic Findings in Chordoma and Chondrosarcoma of the Skull Base

Nicholas J. Volpe, M.D., Norbert J. Liebsch, M.D., John E. Munzenrider, M.D., and Simmons Lessell, M.D.

Review of the clinical features of 48 patients with chordoma and 49 patients with low-grade chondrosarcoma of the skull base disclosed overlapping clinical profiles but distinctive features. Both tumors occurred at all ages but chondrosarcoma tended to occur in the third and fourth decades. Twenty-five (52%) of the patients with chordoma and 24 (49%) of the patients with chondrosarcoma had ocular symptoms (diplopia or visual impairment) as the initial manifestation of the disease. Of the 59 patients (both groups) with diplopia, the diplopia was initially intermittent in 25 (42%). Headache and diplopia from an insidious abducens nerve palsy was most common in both groups. Abducens nerve palsy occurred in 22 (46%) of the patients with chordoma and 23 (47%) of the patients with chondrosarcoma. Normal examination results were more common in patients with chordoma, whereas visual loss, facial numbness, and multiple cranial neuropathies were more common in patients with chondrosarcoma. The similarities in the clinical features of these tumors reflect their common origin at the central skull base and the vulnerability of the abducens nerves at that site. The differences reflect the tendency of chordomas to originate from the clivus and chondrosarcomas to originate from the temporal bone.

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From the Department of Ophthalmology, Harvard Medical School and the Massachusetts Eye and Ear Infirmary, Boston, Massachusetts (Drs. Volpe and Lessell); and the Department of Radiation Oncology, Harvard Medical School, Massachusetts General Hospital and the Harvard Cyclotron Laboratory (Drs. Liebsch and Munzenrider), Boston, Massachusetts.

Reprint requests to Simmons Lessell, M.D., Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114.

CHORDOMAS originate from notochordal rests, whereas chondrosarcomas originate from the embryonal cartilage that escapes resorption during endochondral ossification. Despite their unique cellular origins, chordomas and chondrosarcomas that originate at the central base of the skull share many symptoms and signs, including visual loss and diplopia. Distinguishing between these tumors is difficult radiologically and histologically, and impossible clinically.

Subjects and Methods

We identified 48 (24 male and 24 female) patients with skull-base chordoma and 49 (26 male and 23 female) patients with skull-base chondrosarcoma in the computerized database of the Neuro-ophthalmology Unit of the Massachusetts Eye and Ear Infirmary who had been examined since 1985. Forty-eight of the patients with chordoma and 46 of the patients with chondrosarcoma were white.

Except for three patients who were referred initially to the Neuro-ophthalmology Unit, all had been seen elsewhere and then referred to the Department of Radiation Oncology, Massachusetts General Hospital and the Harvard Cyclotron Laboratory for combined megavoltage x-ray and proton beam irradiation. At the time of the neuro-ophthalmic examination, every patient had radiologic evidence of residual tumor but was free of metastases.

We abstracted and tabulated the following information from each patient's chart: age, age at diagnosis, pathologic diagnosis, first symptom, and duration of symptoms before diagnosis. Information on the duration of symptoms was not available in 11 cases. The presence or absence of headache, diplopia, intermittent diplopia, decreased vision, and facial numbness

before diagnosis was tabulated for each patient. This information was unavailable in two of the patients with chondrosarcoma. Intermittent diplopia was defined as episodes of diplopia separated in time, not diplopia occurring only in certain positions of gaze. The results tabulated for the initial examination (unavailable for two patients with chordoma and five patients with chondrosarcoma) were based on the records of referring physicians. The interval between manifestation and our examination, in the referred patients, ranged from one month to 15 years. The median interval was only three months and in 77 patients was six months or less. Neuroimaging findings were available on 45 patients with chordoma and 40 patients with chondrosarcoma. Eleven of the chondrosarcomas were clivus-based, 19 were at the petrous portion of the temporal bone, nine were parasellar, and one originated in the ethmoid and sphenoid sinuses. All chordomas were in the midline involving the spheno-occipital bone.

Complete neuro-ophthalmic examination included measurement of visual acuity, color vision, exophthalmometry, visual fields, ocular motility, pupil examination, and ophthalmoscopy. Visual fields were performed either on the Goldmann perimeter or on the Humphrey automated perimeter.

Results

The average age at the time of tumor diagnosis was 41.3 years for the patients with chordoma and 36.1 years for the patients with chondrosarcoma. Median age at diagnosis was 44 years in the chordoma group, and cases were distributed evenly over the age range of 6 to 78 years. However, the median age for the patients with chondrosarcoma was 33 years, and although the tumor was manifest at all ages, there was a clustering of cases in the third and fourth decades. Twenty-seven (55%) of the 49 patients with chondrosarcoma were between 21 and 40 years old when the diagnosis was made.

The average interval between the first symptom related to the tumor and diagnosis was 14.6 months for patients with chordoma and 23.5 months for patients with chondrosarcoma. Although the average in the patients with chondrosarcoma was increased by four patients with a duration of greater than eight years, the median was also higher in the patients with chondrosarcoma (eight months, compared to four months in the patients with chordoma [Table 1]).

TABLE 1
INTERVAL BETWEEN THE ONSET OF SYMPTOMS AND DIAGNOSIS OF CHORDOMA OR CHONDROSARCOMA

TIME INTERVAL	CHORDOMA (N = 45)	CHONDROSARCOMA (N = 41)
	NO. (%)	NO. (%)
< 1 Mo	12 (27)	10 (24)
< 3 Mos	9 (20)	5 (12)
< 6 Mos	4 (9)	3 (7)
< 1 Yr	5 (11)	7 (17)
< 3 Yrs	12 (27)	9 (22)
< 5 Yrs	2 (4)	3 (7)
< 10 Yrs	1 (2)	3 (7)
> 10 Yrs	0 (0)	1 (2)

In most patients diplopia or headache indicated the presence of the tumor. Sixteen (33%) of the 48 patients with chordoma developed diplopia as their first symptom; 17 (35%) had headache initially; and in eight (17%) patients these symptoms developed simultaneously. Only one patient initially had decreased visual acuity. Other initial symptoms in patients with chordoma were difficulty with speech and swallowing, decreased hearing, facial weakness, blackouts and unsteadiness, dysmenorrhea, and dizziness. Sixteen (33%) of the 49 patients with chondrosarcoma developed diplopia as their first symptom, 14 (29%) had headache initially, and in five (10%) patients these symptoms developed simultaneously. Three patients with chondrosarcoma had visual loss initially. In the patients with chondrosarcoma, there was a wide variety of other symptoms that either occurred alone or with the headaches and diplopia. These included dizziness, nausea and vomiting, tinnitus, recurrent ear clogging, hoarseness and dysphagia, shoulder weakness, decreased libido, galactorrhea, facial weakness, arm and leg tingling, and hearing loss.

At the time of diagnosis, 32 (67%) of the patients with chordoma had developed headache and 26 (54%) had developed diplopia (Table 2). In 12 of the 26 patients with diplopia, the diplopia was intermittent. Twenty-three (47%) of the 49 patients with chondrosarcoma had developed headache by the time of diagnosis and 33 (67%) had developed diplopia. Intermittent diplopia was reported in 13 of the 33 patients. Nine patients in each group had neither headaches nor diplopia before diagnosis.

TABLE 2
COMMON SYMPTOMS REPORTED BEFORE TUMOR DIAGNOSIS

SYMPTOM	CHORDOMA (N = 48)	CHONDROSARCOMA (N = 47)
	NO. (%)	NO. (%)
Headache	32 (67)	23 (49)
Diplopia	26 (54)	33 (70)
Intermittent diplopia	12 (25)	13 (28)
Decreased visual acuity	4 (8)	6 (13)
Facial numbness	1 (2)	11 (23)
Decreased hearing/tinnitus	1 (2)	4 (9)
Facial weakness	1 (2)	5 (11)
Dysphagia/dysarthria	4 (8)	4 (9)

Other symptoms reported by patients before diagnosis are summarized in Table 2. Facial numbness was more prevalent in patients with chondrosarcoma, reported by 11 (22%) patients as compared to only one patient with chordoma. Facial weakness and decreased hearing or tinnitus were also more frequently reported by patients with chondrosarcoma.

The most prevalent deficit was an abducens nerve palsy, which occurred in 22 (46%) patients with chordoma (Table 3). Fourteen (29%) patients had an isolated, unilateral abducens nerve palsy and three (6%) had a bilateral abducens nerve palsy at the time of diagnosis. An abducens nerve palsy was associated with decreased visual acuity in two patients and with trigeminal nerve sensory deficits in two others. One patient had a combined unilateral oculomotor, trochlear, and abducens nerve palsy. One patient had isolated trochlear nerve involvement and three had isolated oculomotor nerve palsy. No patients had involvement of the facial or acoustic cranial nerves initially. Fifteen (31%) of the patients with chordoma were free of neurologic signs at the time of tumor diagnosis, and in two patients this information was not available.

Four (8%) patients with chordoma had initial visual loss (two had associated abducens nerve palsy). The pattern of the visual field loss differed in each patient: central scotoma, altitudinal defect, junctional scotoma, and bitemporal hemianopsia. In two patients visual acuity was better than 20/30, and in two it was worse than 20/200 initially. Both patients who had signs of increased intracranial pressure were children (ages 6 and 13 years, respectively). These signs accounted for all patients with chordoma except one who had accessory and hypoglossal nerve palsies.

An abducens nerve palsy was the most frequent cranial mononeuropathy occurring as an isolated sign in 15 (31%) patients with chondrosarcoma. Other cranial nerves involved initially are summarized in Table 3. More patients with chondrosarcoma had multiple cranial nerve involvement, compared to the patients with chordoma. Nine (18%) patients had trigeminal nerve involvement and six (12%) had an isolated oculomotor nerve palsy. The facial nerve was involved in four (8%) patients and the acoustic in only one. Of the three patients

TABLE 3
SUMMARY OF THE NUMBER OF PATIENTS WITH INVOLVEMENT OF EACH CRANIAL NERVE

CRANIAL NERVE	CHORDOMA (N = 48)		CHONDROSARCOMA (N = 49)	
	INITIAL	PRERADIATION	INITIAL	PRERADIATION
	NO. (%)	NO. (%)	NO. (%)	NO. (%)
Optic*	4 (8)	5 (10)	3 (6)	11 (22)
Oculomotor	4 (8)	6 (13)	10 (20)	13 (27)
Trochlear	2 (4)	4 (8)	2 (4)	3 (6)
Trigeminal	2 (4)	9 (19)	7 (14)	16 (33)
Abducens	22 (46)	19 (40)	23 (47)	23 (47)
Facial	0 (0)	1 (2)	4 (8)	7 (14)
Acoustic	0 (0)	0 (0)	1 (2)	5 (10)
Glossopharyngeal, vagus, accessory, or hypoglossal	1 (2)	2 (4)	3 (6)	7 (14)

*Includes patients with chiasmal and optic tract lesions.

with visual loss, two had central field defects and the third had a combined altitudinal and temporal defect. In two patients the visual acuity was still better than 20/30, and in the third, visual acuity had decreased to hand motions before diagnosis. Only three (6%) patients with chondrosarcoma had normal examination results.

Except for the three patients with chordoma who came directly to the neuro-ophthalmology unit, patients were examined after at least one surgical procedure. Cranial nerve involvement found at follow-up is summarized in Table 3. Sixteen (33%) patients with chordoma had normal results on follow-up examination. Ten (21%) of the patients with chordoma who had normal results on examination initially continued to have normal results after surgery. Normal examination results in the other six were accounted for by recovered abducens nerve palsies in three, recovered oculomotor nerve palsy in one, and two patients recovered from increased intracranial pressure. Five patients who initially had normal results from examination subsequently developed deficits. These included one patient with decreased visual acuity, two with trigeminal nerve hypesthesias, one with oculomotor, trochlear, and trigeminal nerve dysfunction, and one with a hypoglossal nerve palsy. In all, 34 (71%) of the patients were either unchanged or improved when compared to the time of initial examination. Twelve patients (25%) either had new deficits or increased severity of existing deficits. It was not possible to determine if new deficits were consequent to surgery. Three of the four patients with decreased visual acuity (exact initial information was unavailable on the fourth) improved after surgery.

Seven (14%) patients with chondrosarcoma had normal results on follow-up examinations Only one of these patients, who initially had decreased libido, started with normal results of cranial nerve examination. Three patients recovered from abducens nerve palsy (one bilateral) and the others recovered from hypoglossal nerve palsy, trigeminal and abducens nerve palsy, and trochlear nerve palsy. In three other patients who initially had normal examination results, a hypoglossal nerve deficit, an acoustic nerve deficit, and an oculomotor, trigeminal, and abducens nerve deficit developed. Of the three patients who initially had impaired visual acuity, one improved, one worsened, and the other was unchanged. However, new visual deficits were identified in eight additional patients. Eight of the 11 had monocular deficits. These were characterized by optic atrophy associated with central, altitudinal, or nasal field loss. Two patients had homonymous hemianopsia (presumed secondary to optic tract compression), and one patient had a bitemporal hemianopsia. In three patients visual loss was the only deficit but in eight others there were multiple cranial neuropathies including involvement of the oculomotor nerve in five patients, trigeminal nerve in three patients, the abducens nerve in six patients, the facial nerve in two patients, and the glossopharyngeal, vagus, and hypoglossal nerves in one patient. Involvement of each of the cranial nerves is summarized in Table 3.

Twenty-five (57%) of the 44 patients with chondrosarcoma (no initial examination results were available on five patients) were the same or better on follow-up examination after surgery and before radiation therapy. Nineteen (43%) of the patients either had increased density of existing deficits or new deficits.

Discussion

Together chordoma and chondrosarcoma constitute less than 1% of intracranial tumors.[1-4] In several large reviews of patients with intracranial tumors, chordomas were found in 0.1% to 0.7% of patients.[5-8] Chondrosarcomas represent less than 0.2% of all intracranial tumors and 6.0% of skull-base tumors.[4,9] By 1985, only 50 cases had been identified in the world's literature.[10] About three fourths of chordomas and chondrosarcomas occurring intracranially originate at the base of the skull.[4]

Both tumors can manifest at any age. Chordomas typically become symptomatic in the third to fifth decade. In reported series the mean age at initial manifestation was 38 years,[3,11] 44 years,[12] and 50 years[13] for patients with chordoma. In our series the mean age was 41.3 years at the time of diagnosis and cases were distributed evenly in all decades. Three cases occurred in children under the age of 10 years. The oldest patient in our chordoma series was 78 years old. Although not common, cases of chordoma have been reported in patients in the seventh and eighth decades.[14]

Chondrosarcomas most frequently occur in young adults and seem to be most frequent in the second and third decades of life.[15] In the 50 cases reviewed by Hassounah and associ-

ates,[10] 30 occurred in the second and third decades of life and the youngest reported case was in a 7-year-old,[16] and the oldest in a 65-year-old patient. Another case in a 69-year-old patient has since been reported.[17] In our patients with chondrosarcoma the mean age was 36.1 years, and the median age was 33 years, both lower than in patients with chordoma. There was a clustering of cases (55%) in the third and fourth decades and no cases occurred in the first and eighth decades.

Although several series have reported a male preponderance of up to 70%[3,6,11-13,18-23] in patients with chordoma, we found the genders equally affected. As in our patients there has been no recognized gender predilection for chondrosarcoma.[2,10]

Chordomas and chondrosarcomas grow slowly and therefore symptoms tend to develop insidiously. Amendola and associates[13] found that symptoms had been present for more than one year in all 21 of their patients with chordoma. In various series, the mean duration from first symptom to tumor diagnosis was 16 months,[23] 20 months,[19] and 41 months.[3] The range is wide and extends from eight weeks of symptoms,[12] to 16 years.[3] The interval between onset of symptoms and diagnosis is longer in the slower growing chondroid variant of chordoma.[23] The average duration of symptoms for our patients with chordoma in this series was 14.6 months. The average was increased by a few patients who had a prolonged interval between onset of symptoms and detection of the tumor markedly delayed manifestation. The median duration of symptoms was far shorter at four months. This shorter interval between the onset of symptoms and detection of the tumor in our patients may reflect the increasing use of computed tomography and magnetic resonance imaging.

Review of 26 cases of cranial chondrosarcoma in the literature[1,2,10,17,24-30] showed a duration of symptoms before diagnosis that ranged from one month to six years. The median duration of symptoms was two years and the mean was 26 months in these patients. We found a mean of 23.5 months in our patients and a median of eight months.

Headache and diplopia are the most commonly reported initial symptoms.[10-13,19,31-33] Bagan and Hollenhorst[12] reported the largest series (63 patients) that specified the neuro-ophthalmic manifestations of chordoma. They found that diplopia was the most common initial symptom, present in 70% of patients. Heffelfinger and associates[11] found that 90% of their patients had diplopia and half had headaches. Raffel and associates[19] found 12 of their 26 patients initially had diplopia and 15 had headaches. In other series, headaches have been reported in up to 90% of patients.[14,21] This finding is in agreement with ours.

In Bagan and Hollenhorst's series,[12] 39 (61%) of 63 patients had diplopia or decreased visual acuity at the time of diagnosis. In our series, 25 (52%) patients with chordoma had diplopia or decreased visual acuity, and 26 (54%) had these symptoms before diagnosis. The slightly lower prevalence of ocular symptoms may reflect the earlier detection of the tumor in patients who suffer from only headache. Of the patients with chondrosarcoma, 24 (49%) had ocular symptoms as their first manifestation of their tumor. However, at the time of diagnosis, 38 (78%) patients had either diplopia or decreased visual acuity. Patients with chondrosarcoma seem to progress more rapidly from headache to cranial nerve involvement.

Patients with chordomas and chondrosarcomas may have only nasopharyngeal symptoms.[34,35] These symptoms include nasal obstruction, eustachian tube obstruction, throat fullness, and epistaxis. A nasal mass is frequently seen.[11,35,36] Batsakis and Kittleson[36] reported five cases of chordoma with nasopharyngeal symptoms that included nasal speech, hypoacusis, paralysis of tongue, vertigo, nasal obstruction, dysphagia, and dysarthria. In another series of 20 patients with chordoma, Perzin and Pushparaj[35] found nasal obstruction and decreased hearing to be the most common symptoms in tumors with nasopharyngeal manifestation. Of these patients 40% to 90% will have a mass on careful examination of the pharynx.[21,35,36] In our series, only four patients with chordoma and four patients with chondrosarcoma had dysphagia and dysarthria. In two cases, diagnosis was made after biopsy of pharyngeal masses.

Pain or hypesthesia in the distribution of the trigeminal nerve and symptoms resulting from facial and acoustic nerve involvement can also be the initial manifestations. Although these symptoms have been described in both tumors,[1,37] we found the incidence of these to be much higher in the patients with chondrosarcoma. Facial numbness occurring early in the development of tumor symptoms was more likely to occur in patients with chondrosarcoma. Facial weakness, decreased hearing, and tinnitus all occurred more commonly in pa-

tients with chondrosarcoma. The tendency of chondrosarcomas to originate from the temporal bone and to affect the trigeminal, facial, and acoustic nerves likely explains this difference.

In both groups of patients, initial visual loss was rare. This was in contradistinction to previous reports in which visual loss was found in 16%,[12] 19%,[19] 25%,[11] 29%,[20] and 50%[21] of patients at the time of the diagnosis of the tumor. Only one (2%) of our patients with chordoma initially had decreased visual acuity, and four (8%) developed decreased visual acuity before diagnosis. Visual loss was slightly more common in patients with chondrosarcoma and was the first symptom in three patients and developed before diagnosis in another three patients. On subsequent examination, visual loss resulted from compression of the optic nerve or chiasm in both types of tumors but both cases with optic tract involvement were chondrosarcomas. The patients in this series had gradual loss of visual acuity, but instances of precipitous loss of visual acuity, simulating optic neuritis, have been reported.[28,38]

The two tumors are radiographically difficult to distinguish. Computed tomography typically shows bone destruction, contrast enhancement, and tumor calcification.[2,10,39,40] Calcification is more common in the chondroid variant of chordoma.[11] Magnetic resonance imaging features of both tumors include prolonged T_1 and T_2 relaxation times resulting in hypointensity on T_1 and hyperintensity on T_2.[41] Angiographically, both tumors are usually avascular but in a subset of patients with chondrosarcoma, often with mesenchymal histopathologic findings (not included in this series), they are highly vascular and can mimic arteriovenous malformations.[37]

Occasionally the clinical manifestation of the tumor will be associated with a radiographically undetectable lesion. Before diagnosis, eight of our patients with chondrosarcoma and four patients with chordoma had normal computed tomographic scans. These had been from eight months to several years before tumor diagnosis. In all but one patient the imaging study was performed to evaluate an abducens nerve palsy. Four of these patients with abducens nerve palsy underwent strabismus surgery, one to 15 years before recognition of the tumor. This manifestation of chronic, isolated abducens nerve palsies from tumors at the skull base, that initially go undetected, is well recognized.[42-44] Also, intermittent diplopia from transient recurrent cranial nerve palsies has been reported in chordoma,[45,46] and was common in both groups of our patients. Intermittent cranial nerve dysfunction may reflect the ability of these tumors to interfere transiently with the blood supply to the nerve, cause temporary demyelination, or perhaps cause a compressive conduction block. Both intermittent and chronic isolated cranial mononeuropathies are important clues that should point the clinician to a slowly progressive compressive lesion at the skull base.

Fifteen (31%) of patients with chordoma had normal examination results initially compared to only four (8%) of patients with chondrosarcoma. Abducens nerve palsy was the most common deficit in both groups of patients initially and abducens nerve palsy is the most common finding in most published series.[1,2,12,19,20,31,33,47] Bilateral abducens nerve involvement was seen in both groups of patients. Involvement of the oculomotor, trigeminal, facial, and acoustic cranial nerves was found more often in chondrosarcomas. Excluding the cases of bilateral abducens nerve palsies, 14 (32%) of the 44 patients with chondrosarcoma, compared to six (13%) of the 46 patients with chordoma, had involvement of more than one cranial nerve at the time of initial manifestation. The trend to multiple ipsilateral cranial nerve involvement for patients with chondrosarcoma was also seen on our examination before radiation. On follow-up examination, 29 (60%) of the 48 patients with chordoma had either normal results or oculomotor, trochlear, or abducens nerve palsy. Only 17 (35%) of the patients with chondrosarcomas had these isolated defects. The difference was most noticeable in patients with chondrosarcoma and visual loss. Visual loss was an isolated finding in only three of the 11 patients, and in the eight others multiple cranial nerves were involved. Multiple deficits associated with visual loss were not seen as frequently in patients with chordoma.

Although no single clinical feature of our patients was identified that would distinguish these two unusual tumors, different patterns of cranial nerve involvement occurred in chordoma compared to chondrosarcoma. The embryologic origin of each tumor helps to explain both the similarities and the differences in their clinical behavior. Both notochordal tissue and unossified chondrocranium can persist in the central skull base. Notochordal remnants are rarely found away from the midline in contradistinction to chondrocranium, which forms the entire skull base. Chordomas originate in

the midline but chondrosarcomas can originate in all parts of the skull base. Most patients with skull-base chordomas and chondrosarcomas develop headaches and diplopia. Isolated abducens nerve palsy is the most common deficit for both tumors at initial manifestation. In this setting, given their similar radiographic appearance, the tumors are difficult to distinguish. Although subsequent growth of either tumor can produce any pattern of cranial neuropathy, visual loss, facial numbness, multiple cranioneuropathies, and involvement of the more laterally located oculomotor, trigeminal, facial, and acoustic cranial nerves are more typical of chondrosarcoma. A slower, more indolent course with involvement of fewer cranial nerves was more typical of chordoma. A better understanding of these clinical patterns will help in the design and evaluation of treatment strategies that use both neurosurgery and radiation therapy.

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PERSPECTIVES

Developmental Genes and Ocular Malformation Syndromes

Elias I. Traboulsi, M.D.

How does a fertilized ovum develop into a well-formed human being? What coordinates the fate of genetically identical embryonic stem cells, turning some into limbs and others into eyes or parts thereof? What synchronizes the myriad decision-requiring events in fetal development? What reparative processes exist to compensate for mishaps? What is behind the miracle of the perfect eye and body?

Several families of so-called homeotic genes are responsible for the orchestration and regulation of normal development of biologic systems.[1-3] In the last decade new landmarks have been set in our understanding of embryology with the discovery, among others, of the homeobox independently by McGinnis and associates[4] and Scott and Weiner.[5] The homeobox is a DNA segment, 183 base pairs in length, which codes for a protein that constitutes the DNA binding region or homeodomain of some homeotic gene products. The proteins coded for by homeobox-containing genes regulate DNA transcription by binding to downstream (toward the 3′ end of the gene) genes and also regulate their own production. Homeobox sequences in different homeotic genes within and between genera and species are so similar or conserved that they are likely to have evolved from common ancestral genes by a process of tandem duplication, or side-by-side duplication.[6,7] It is also hypothesized that after duplication, mutations in some respective genes result in diversification of function and specific body segment expressivity. Homeobox-containing genes are arranged in clusters on one or more chromosomes (one in *Drosophila* and four in mouse and man).[8] These genes regulate the development of body segments cephalad to caudad, depending on their location in the gene cluster.[9] The developing embryo at the multiple somite stage consists of a tandem array of duplicated body segments. These primordial segments form different body parts under the control of homeotic genes. There are clear-cut boundaries and synchronized expression of proteins for homeotic genes, coding for example for the development of a thoracic or an abdominal segment in *Drosophila*. Studies in mice and other vertebrates and invertebrates have outlined the pattern of expression of homeotic genes in the developing embryo.[10,11] Targeted disruption of homeotic genes results in severely malformed animals.[12] A superb review of the history of the evolution of our understanding of the function of homeotic genes in *Drosophila* was given by Lewis in his 1991 Albert Lasker Medical Award dissertation.[13]

Like other landmarks in the history of modern medical genetics such as the assignment of daltonism or color blindness to the X chromosome, the linkage of one type of congenital cataracts to the Duffy blood group, and the discovery that retinoblastoma is caused by a recessive cancer-suppressor gene, the visual system has served as a model for the clinical correlation of abnormalities in homeotic genes with malformation syndromes. Early studies on the duplication of developmental genes in *Drosophila* involved flies with ocular abnormalities such as the *Bar*-eyed mutant (small eyes) discovered by Tice in 1913, and the rough-eyed *Drosophila* mutants.[13] Ton and associates[14] recently cloned and characterized a paired box-containing and homeobox-containing gene from the aniridia region on chromosome 11, making aniridia the first well-defined clinical condition that results from alteration of a homeotic gene. The mouse small-eye mutant results from mutations in the paralogue of the human aniridia gene.[15] Further work by Jordan and associates identified mutations in the human PAX6 gene in two patients with sporadic aniridia.[16] More recently Tassabehji and associates[17] and Baldwin and associates[18] have shown that the gene for Waardenburg syndrome (telecanthus, deafness, and abnormal pigmentation) belongs to the HOX family of homeobox-containing genes, and is responsible for neural crest differentiation. It is also believed that the Wolf-Hirschhorn syndrome results from dis-

ruption of homeotic genes on the short arm of chromosome 4[19]; this syndrome features among other abnormalities anterior segment dysgenesis and, in some patients, colobomatous microphthalmos. In two recent studies, a candidate homeotic gene for the X-linked Norrie disease (retinal dysplasia, deafness, and mental retardation in some patients) was cloned and sequenced.[20,21] This candidate gene does not share any sequences with known developmental genes and is thought to belong to a hitherto unidentified family of developmental genes.

Other loops of the unraveling, complex, developmental pathways involve growth factors,[22] retinoic acid[23] and its receptors, zinc finger genes, and a number of as yet unidentified components.[24,25] The orchestration of normal development is formidable, and efforts to elucidate it and its pathologic correlate are ongoing. Developmental ocular diseases and malformations involving candidate developmental genes are numerous,[26] and the approaches for the study of the genetics of these conditions remain to be defined.

From the Johns Hopkins Center for Hereditary Eye Diseases, the Wilmer Ophthalmological Institute, Johns Hopkins Hospital, Baltimore, Maryland.

Reprint requests to Elias I. Traboulsi, M.D., Maumenee 317, 600 N. Wolfe St., Baltimore, MD 21205.

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OPHTHALMIC MINIATURE

Then all the afflicted of Egaja turned up, and wanted medical advice. There was evidently a good stiff epidemic of the yaws about; lots of cases of dūm with the various symptoms; ulcers of course galore; a man with a bit of a broken spear head in an abscess in the thigh; one which I believe a professional enthusiast would call a 'lovely case' of filaria, the entire white of one eye being full of the active little worms and a ridge of surplus population migrating across the bridge of the nose into the other eye, under the skin, looking like the bridge of a pair of spectacles.

Mary Kingsley, *Travels in West Africa*
Rutland, Vermont, Everyman's Library, 1987, p. 121

LETTERS TO THE JOURNAL

Multiple Mitochondrial DNA Deletions in Myo-neuro-gastrointestinal Encephalopathy Syndrome

Donald R. Johns, M.D., Anisa B. Threlkeld, M.D., Neil R. Miller, M.D., and Orest Hurko, M.D.

Departments of Neurology (D.R.J., O.H.) and Medicine (O.H.), and the Wilmer Ophthalmological Institute (A.B.T., N.R.M.), Johns Hopkins University School of Medicine.

Inquiries to Donald R. Johns, M.D., Meyer 6-119, Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21287-7619.

We recently reported the comprehensive clinical and laboratory data on a 26-year-old woman with the myo-neuro-gastrointestinal encephalopathy syndrome.[1] A mitochondrial cause for the patient's disease was proposed on clinical, biochemical, and morphologic grounds. We have extended our initial molecular genetic data on this case to include the presence of multiple mitochondrial DNA deletions in her skeletal muscle.

The patient's skeletal muscle showed histochemical and biochemical evidence of cytochrome c oxidase dysfunction and thus the mitochondrial DNA-encoded genes, cytochrome oxidase subunits II and III, were sequenced in their entirety. No missense mutations were present in either gene. None of the three point mutations in mitochondrial transfer RNAs reported in a patient with a similar syndrome[2] were present in our patient. Most recently we reexamined the gross mitochondrial DNA structure after the presence of multiple mitochondrial DNA deletions was noted in another muscle specimen from our index patient (M. Hirano, M.D., oral communication, Aug. 26, 1992).

Total DNA was extracted from a frozen aliquot of the original quadriceps muscle biopsy specimen and subjected to Southern blotting after digestion with the restriction enzymes *Pvu* II and *Bam* HI. Prolonged exposure of the Southern blot revealed multiple, large scale mitochondrial DNA deletions in relatively low abundance. Indeed the presence of the deleted bands was not appreciated on the original Southern blot under the usual experimental conditions used to detect single mitochondrial DNA deletions. The structure of the deleted mitochondrial DNAs was further analyzed by the use of the widely interspaced primer polymerase chain reaction technique.[3] The molecular structure of two of these deleted mitochondrial DNAs was determined: a 4.591-kilobase deletion from nucleotide position 11,480 (ND4 gene) to 16,071 (displacement-loop) and a 7.663-kilobase deletion from 6,342 (COX I gene) to 14,005 (ND5 gene). The 4.591-kilobase deletion was flanked by a 3/4 nucleotide directly repeated sequence and the 7.663-kilobase deletion was flanked by an 11/11 nucleotide directly repeated sequence.

THE JOURNAL welcomes letters that describe unusual clinical or pathologic findings, experimental results, and new instruments or techniques. The title and the names of all authors appear in the Table of Contents and are retrievable through the Index Medicus and other standard indexing services. Letters must not duplicate data previously published or submitted for publication. Each letter must be accompanied by a signed disclosure statement and copyright transfer agreement published in each issue of THE JOURNAL.

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Multiple mitochondrial DNA deletions have been found in several different neurologic syndromes, including variants of chronic progressive external ophthalmoplegia and recurrent myoglobinuria.[4,5] Both autosomal dominant and autosomal recessive inheritance patterns have been noted, but all patients had ragged red fibers on skeletal muscle biopsy specimens and harbored multiple mitochondrial DNA deletions with similar molecular features. Despite the wide variety of accompanying signs and symptoms, the only prominent gastrointestinal feature was dysphagia in one pedigree.[4]

Myo-neuro-gastrointestinal encephalopathy syndrome should be added to the growing list of neurologic syndromes associated with multiple mitochondrial DNA deletions. We predict that further human diseases will be pathogenetically linked to multiple mitochondrial DNA deletions and that most will have chronic progressive external ophthalmoplegia as an integral feature. However, a number of other organ systems may be involved as well. Our case is unique among cases of multiple mitochondrial DNA deletions because of the association with the myo-neuro-gastrointestinal encephalopathy syndrome and the lack of ragged red fibers in skeletal muscle. The myo-neuro-gastrointestinal encephalopathy syndrome exhibits noteworthy genetic heterogeneity, and determination of the relative frequency of multiple mitochondrial DNA deletions in patients with this syndrome awaits more extensive studies.

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Subconjunctival Silicone Oil After Vitreoretinal Surgery

Amy K. Hutchinson, M.D., Antonio Capone, M.D., and Hans E. Grossniklaus, M.D.

Department of Ophthalmology, Emory University School of Medicine.

Inquiries to Hans E. Grossniklaus, M.D., L. F. Montgomery Eye Pathology Laboratory, Emory Eye Center, 1327 Clifton Rd. N.E., Atlanta, GA 30322.

Complications associated with the use of intraocular silicone oil have been well documented, and extravasation of the silicone oil into the subconjunctival space has been reported.[1,2] The clinicopathologic features of this complication, however, have not been well documented.

A 57-year-old man was examined for severe proliferative vitreoretinopathy and a second recurrence of a retinal detachment in his right eye. He had had an extracapsular cataract extraction and a posterior chamber intraocular lens implant, placement of a scleral buckle, and a vitrectomy for a recurrent retinal detachment. Examination showed visual acuity to be hand motions in the right eye. Ophthalmoscopy showed fixed retinal folds, a prominent area of proliferative vitreoretinopathy, and several large retinal breaks. The patient underwent a second vitrectomy with retinal membrane dissection, photocoagulation, removal of the intraocular lens and silicone oil injection. Two months postoperatively, visual acuity in the right eye was 20/400 and the retina remained attached; however, a diffuse bulbar conjunctival subepithelial infiltrate was noted. The infiltrate coalesced over a period of several weeks to form transparent, firm subepithelial droplets (Fig. 1). The patient underwent removal of the intraocular silicone oil and excision of the involved conjunctiva. Histopathologic examination of the conjunctival specimen showed fibrovascular tissue infiltrated with chronic inflammatory cells including foreign body giant cells. Vacuolated spaces were identified that corresponded to extruded silicone oil (Fig. 2). Ultrastructural

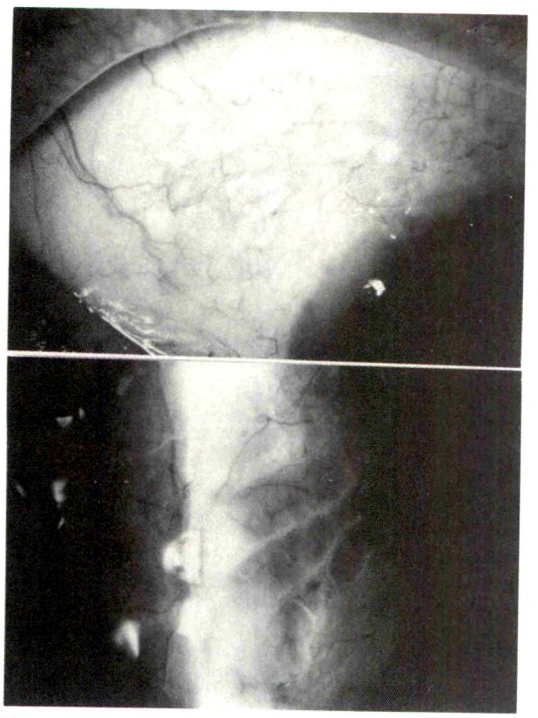


Fig. 1 (Hutchinson, Capone, and Grossniklaus). Top, External examination shows bulbar conjunctival subepithelial accumulations of transparent material. Bottom, Closer inspection discloses the droplike appearance of the material.

examination confirmed the presence of intracellular and extracellular accumulations of silicone oil droplets.

We have seen another patient with subconjunctival silicone oil after retinal detachment surgery. As with our first patient, the lesion in our second patient initially appeared as a diffuse subepithelial mass infiltrate that coalesced into transparent droplets, suggesting a pattern in the clinical evolution of subconjunctival silicone oil.

There are several cystic and noncystic subepithelial bulbar conjunctival masses in the clinical differential diagnosis of subconjunctival silicone oil. The cystic entities include epithelial inclusion cyst, lymphangiectasia, Leber's lymphangiectasia hemorrhagica, and cystic amelanotic nevi. Noncystic subepithelial masses that may be similar in clinical appearance to subepithelial silicone oil include lymphoma, myxoma, vascular tumors, and other rare lesions.[3] The clinical history and findings from external examination can help exclude these lesions.

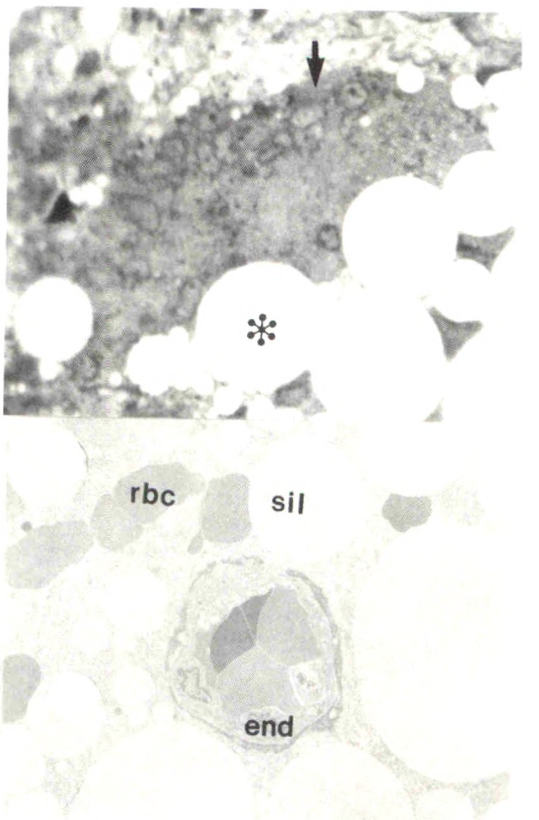


Fig. 2 (Hutchinson, Capone, and Grossniklaus). Top, The conjunctival biopsy specimen exhibits extracellular vacuoles (asterisk) and occasional foreign body giant cells (arrow) (toluidine blue, × 160). Bottom, Ultrastructural features of the biopsy specimen include endothelial-lined (end) vascular channels, extracellular erythrocytes (rbc), and silicone oil droplets (sil) (× 1,900).

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A Diode Laser Mounted on a Slit Lamp for Ophthalmic Photodynamic Applications of Phthalocyanine

Leonidas P. Naoumidis, Ph.D., Miltiades K. Tsilimbaris, M.D., Anthimos Georgiades, Ph.D., and Ioannis G. Pallikaris, M.D.

Eye Vardinoyannion Institute of Crete, Department of Ophthalmology, School of Health Sciences, University of Crete.

Inquiries to Ioannis G. Pallikaris, M.D., Eye Vardinoyannion Institute of Crete, Department of Ophthalmology, School of Health Sciences, University of Crete, P.O. Box 1352 Heraklion, Crete, 711 10 Greece.

Photodynamic therapy has been applied successfully in ophthalmology to experimental treatment of tumors as well as to experimental photothrombosis of normal and new vessels.[1,2] Chloroaluminum sulfonated phthalocyanine is a new photosensitizing agent that has produced good experimental results in photodynamic treatment of endobulbar melanoma and in iris neovascularization photothrombosis.[3,4] Recently, in ophthalmic photodynamic applications of this dye, an argon-pumped 675-nm dye laser operating at low power settings has been used as a light source for its activation. The use of this type of laser puts the intensive experimentation with phthalocyanine at a relative disadvantage because of the relatively complex and costly equipment required. For this reason, we used a low-power 675-nm diode laser as an alternative to the dye laser in photodynamic applications of phthalocyanine.

The diode laser used (675-nm wavelength, up to 7-mW output in the continuous wave mode) was a simple serial model (Laser Diode Module, LDA 2015, Laser 2000 GmbH, Puchheim, Germany), produced for general use. The laser was supplied with a variable-distance focusing system, which proved to be useful in ophthalmic photodynamic applications.

Because of the low intensity of laser radiation normally used in ophthalmic photodynamic applications, relatively long irradiation times are often necessary to achieve the desired therapeutic effect. Thus, the construction of a laser unit for photodynamic therapy must provide high mechanical and output stability during the long laser exposure, and also the possibility to control the irradiation process microscopically.

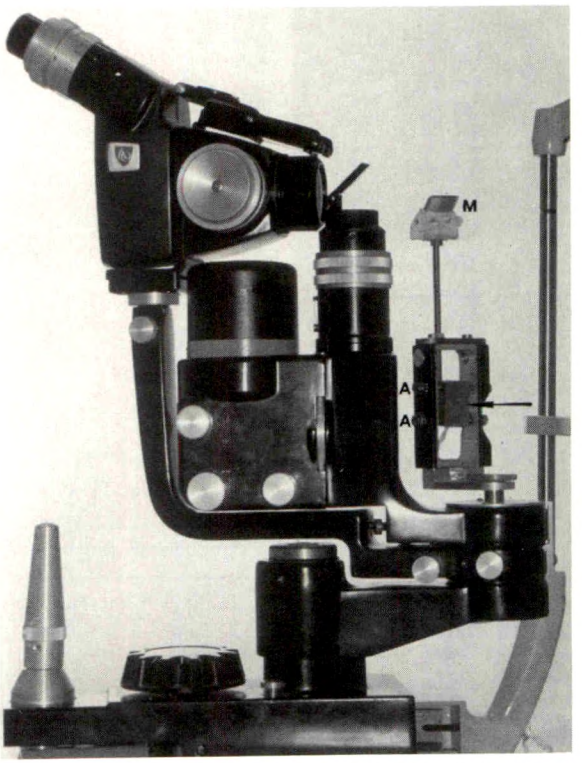


Fig. 1 (Naoumidis and associates). General view of the diode laser mounted on the slit lamp (laser housing is indicated by an arrow). The letter M indicates the deflecting mirror; the letter A indicates the adjustment screws.

To meet these requirements, a simple construction of the phototherapeutic diode laser unit was devised, in which the diode laser compartment was designed as a separate module, which could be easily installed on the slit lamp, similar to such slit lamp accessories as the Goldmann applanation tonometer (Fig. 1). The laser housing was incorporated inside a modified container of a Goldmann tonometer (Model 11589 Applanation Tonometer, American Optical Scientific Instruments, Buffalo, New York) and provided a manipulation freedom similar to that of the slit illuminator. The adjustment screws (Fig. 2) simplified the installation process, and allowed alignment of the laser beam at any step of the treatment procedure. The design permitted accurate control and fixation of the laser beam in relation to the optical axis. The variable-distance focusing system facilitated the final adjustment of the laser

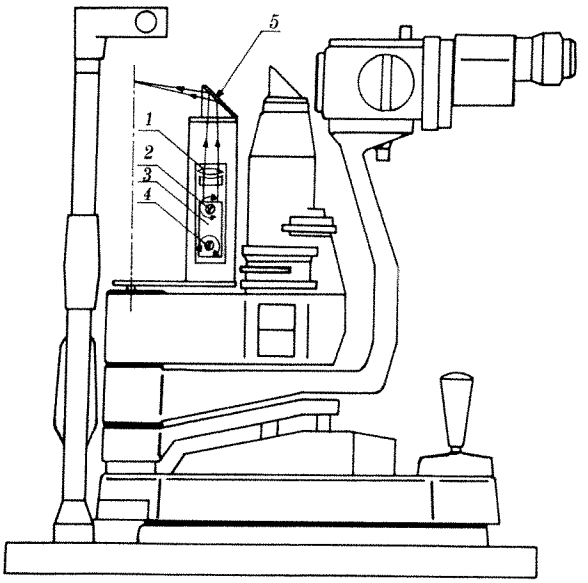


Fig. 2 (Naoumidis and associates). Schematic drawing of the diode laser module installed on the slit lamp; 1 indicates the diode laser housing; 2 and 3 indicate the adjustment screws; 4 indicates the laser beam focusing system; and 5 indicates the deflecting mirror.

beam in relation to the focal plane of the slit lamp.

The installation and removal of the diode laser module are simple, do not need any specialized personnel, and do not create any problems in the conventional use of the slit lamp. The construction is low in cost and is easy to reproduce: a deflecting mirror was the only optical element used in addition to the standard optics of the slit lamp and of the diode laser.

This diode laser unit has been effectively used for experimental induction of photothrombosis in normal rabbit choroidal vessels in combination with phthalocyanine,[5] and we believe it can be an effective and low-cost alternative for activation of phthalocyanine in ophthalmic photodynamic applications.

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Unesterified Cholesterol in Granular, Lattice, and Macular Dystrophies

Merlyn M. Rodrigues, M.D., Howard S. Kruth, M.D., Sankaran Rajagopalan, M.D., and Kelly Jones

Department of Ophthalmology, University of Maryland (M.M.R., S.R., K.J.); and Section of Experimental Atherosclerosis, Molecular Disease Branch, National Heart, Lung and Blood Institute (H.S.K.). Dr. Rodrigues is a Senior Scientific Investigator, Research to Prevent Blindness, Inc., New York, New York.

Inquiries to Merlyn M. Rodrigues, M.D., University of Maryland at Baltimore, Ophthalmic Pathology Laboratory, 10 S. Pine St., M.S.T.F., Room 5-00B, Baltimore, MD 21201.

Heritable corneal opacities may be caused by disorders of lipid metabolism, as well as by those of other molecules.[1] Unesterified cholesterol constitutes an important component of the lipid deposits in Schnyder's corneal crystalline dystrophy.[2] Alterations in corneal phospholipid occur in granular corneal dystrophy.[3] In the most common form of macular corneal dystrophy known as type I disease, there is a defect in keratan sulfate biosynthesis.[4,5] Lattice corneal dystrophy is associated with abnormal accumulation of amyloid. We investigated whether an abnormal accumulation of unesterified cholesterol occurs in granular, macular, and lattice dystrophies.

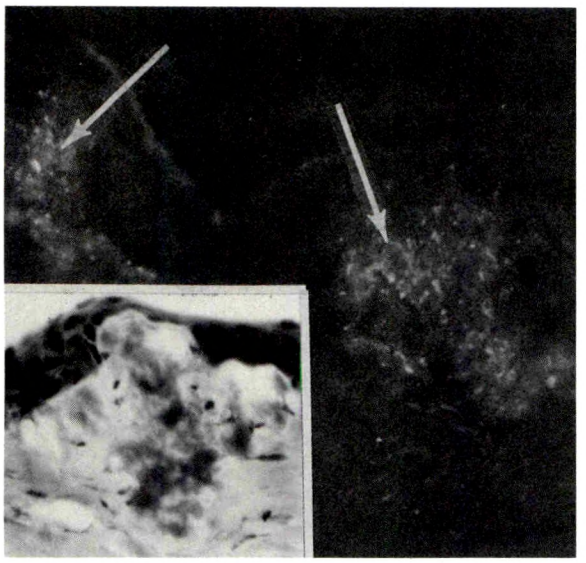


Fig. 1 (Rodrigues and associates). Granular dystrophy. The subepithelial deposits display multiple fluorescent stippled areas (arrows) (filipin stain, × 320). Inset, A similar deposit stained with Luxol fast blue (× 200).

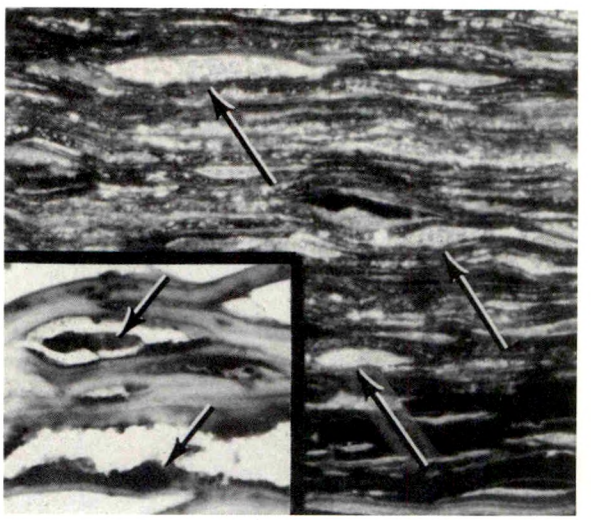


Fig. 2 (Rodrigues and associates). Macular dystrophy. The stroma shows prominent fusiform aggregates of unesterified cholesterol (arrows) (filipin stain, × 320). Inset, Abnormal accumulation of glycosaminoglycan in areas corresponding to filipin staining (arrows) (colloidal iron stain, × 200).

Frozen sections of formalin-fixed tissue from three cases each of granular dystrophy, lattice dystrophy type I, and macular dystrophy type I were stained with filipin as we previously described.[2] Propylene glycol extraction was performed before filipin staining. Frozen sections were also stained with periodic acid-Schiff, Congo red, alcian blue, colloidal iron, and luxol fast blue. Normal corneas from age-matched control subjects were included.

In all cases, extracellular deposits were observed. In granular dystrophy, filipin staining after propylene glycol extraction disclosed scattered, stippled staining of the deposits in the superficial half of the cornea (Fig. 1). In lattice dystrophy, the staining was more fusiform, and correlated with areas of Congo red reactivity. The extracellular deposits involved the superficial half of the cornea. In macular dystrophy, the staining was more diffuse and corresponded to alcian blue and colloidal iron reactivity (Fig. 2). Panstromal staining was noted, without involvement of Descemet's membrane and corneal endothelium.

The deposits in Schnyder's dystrophy have been shown to consist of predominantly unesterified cholesterol, as well as neutral lipid and triglycerides.[2] Granular dystrophy has been characterized by an accumulation of phospholipid and microfibrillar protein and consists of electron-dense deposits of homogeneous or finely fibrillar material that mainly involve the stroma, but can also affect the epithelium.[3] The deposits stain positive for phospholipid with luxol fast blue and are delineated with Masson's trichrome.[3] In our cases of granular dystrophy, the unesterified cholesterol could be masked or sequestered because of excess phospholipid accumulation, since the filipin staining was observed only after propylene glycol extraction. In macular dystrophy, the deposits display greater heterogeneity and in the type I form, a defect in keratan sulfate biosynthesis has been detected in which keratan sulfate proteoglycan is undersulfated or lacks sulfation.[4]

In addition to the primary abnormality of phospholipid in granular dystrophy, amyloid in lattice dystrophy, and defective proteoglycan in macular dystrophy, we detected a secondary accumulation of unesterified cholesterol in these disorders. The detection of filipin staining in granular, lattice, and macular dystrophies suggests that these diseases could be associated with an abnormal processing of unesterified cholesterol. The unusual accumulation of cholesterol in each of these conditions may reflect entrapment of cholesterol by the phospholip-

ids, amyloid, and proteoglycans that accumulate in these dystrophies.

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Ciprofloxacin Therapy of *Mycobacterium chelonae* Keratitis

David G. Hwang, M.D., and Roderick Biswell, M.D.

Cornea Service, Department of Ophthalmology, University of California, San Francisco. This work was supported by That Man May See, Inc., San Francisco, California, and Research to Prevent Blindness, New York, New York.

Inquiries to David G. Hwang, M.D., Cornea Service, Department of Ophthalmology, University of California, San Francisco, 10 Kirkham St., San Francisco, CA 94143-0730.

Keratitis caused by the atypical mycobacterium, *Mycobacterium chelonae (chelonei)*, manifests as an indolent, recalcitrant deep keratitis that can follow trauma or surgery.[1-4] Since atypical mycobacteria are resistant to most antibiotics, treatment of atypical mycobacterial infections is difficult. Although amikacin has been described as the treatment of choice for *M. chelonae* and other atypical mycobacteria,[1,3] treatment failures may occur despite good in vitro susceptibility.[2] Since fluoroquinolones such as ciprofloxacin have fair to excellent in vitro activity against atypical mycobacteria,[5] these antibiotics may be good candidates for the treatment of atypical mycobacterial keratitis. We encountered a case of *M. chelonae* keratitis that occurred after radial keratotomy in which an initially poor response to treatment with fortified amikacin was reversed with the addition of topical ciprofloxacin.

A healthy 45-year-old woman underwent eight-incision radial and two-incision transverse keratotomy of both eyes, two weeks apart. Cold sterilization was used to disinfect the keratotomy knife. The patient did well on a postoperative regimen of tobramycin and dexamethasone until two months postoperatively, when a small, deep stromal infiltrate was noted adjacent to an inferior transverse incision in an otherwise uninflamed right eye. Initial cultures taken from the incision were negative for bacteria and fungi. Tobramycin and dexamethasone were continued, and brief courses of trimethoprim-polymyxin B and ciprofloxacin were initiated without effect on the continued slow progression of the infiltrate. At the time of referral four months postoperatively, the patient's best-corrected visual acuity in the right eye was 20/30−. A white, deep stromal 3.0-mm infiltrate with irregular, multilobular edges was present adjacent to the radial cut at the 7:30 o'clock meridian and the inferior transverse incision. The overlying epithelium was intact and signs of inflammation were minimal (Figure). The left eye was unaffected.

Because of the suspicion of a slowly progressive deep infectious keratitis, the patient underwent corneal biopsy. In order to gain access to the involved deep stroma for culture and debridement while preserving the uninvolved anterior lamellae, the inferior transverse incision was extended temporally until it intersected the radial incision at the 7:30 o'clock meridian, allowing a triangular flap of uninvolved corneal tissue overlying the infiltrate to be elevated by careful dissection. After biopsy and debridement of the infiltrated stroma at the bed of the dissection, the flap was reapproximated with interrupted sutures. Smears of the infiltrate showed acid-fast bacilli, and cultures on

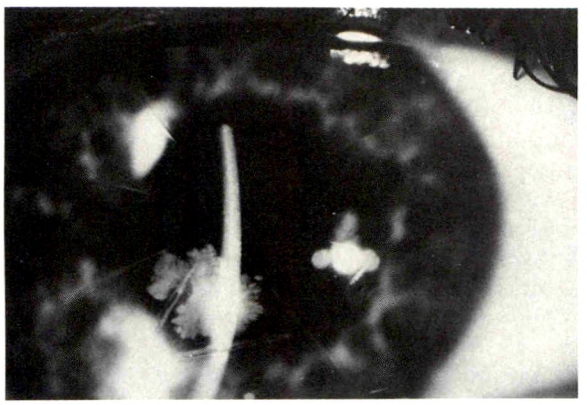


Figure (Hwang and Biswell). Deep, indolent corneal infiltrate four months after radial keratotomy, caused by *M. chelonae*.

blood agar and Lowenstein-Jensen medium grew *M. chelonae*, subspecies *abscessus*.

The patient was given fortified amikacin (50 mg/ml) every hour, supplemented with a collagen shield. Because the infiltrate progressively continued to worsen despite three weeks of fortified amikacin therapy, hourly ciprofloxacin 0.3% was added. Within two weeks the patient began showing signs of clinical improvement. Three weeks after initiation of ciprofloxacin, the patient decided to discontinue the ciprofloxacin but continued the amikacin. When seen ten days later, she had developed increased infiltrate and a new hypopyon. The infiltrate and associated inflammation improved two to three weeks after ciprofloxacin therapy was reinstated. Susceptibility results for the organism indicated intermediate sensitivity to amikacin (minimum inhibitory concentration [MIC] = 32 μg/ml) and good sensitivity to ciprofloxacin (MIC = 2 μg/ml). Amikacin and ciprofloxacin were gradually tapered but continued for a total of one year to guard against recurrence. At the conclusion of treatment, best spectacle-corrected visual acuity in the right eye was 20/25, and a vascularized scar was present in the area of previous infiltrate. There has been no evidence of recurrence to date.

Robin and associates[3] and Matoba and associates[4] described *M. chelonae* keratitis occurring after radial keratotomy. As in the two previously reported cases of Robin and associates,[3] the diagnosis was established by corneal biopsy. In our case, a lamellar flap corneal biopsy technique was used to spare the anterior, uninvolved lamellae. Similar to one of the patients described by Robin and associates,[3] our patient did not respond to amikacin alone (despite moderate in vitro susceptibility to amikacin). However, our patient did improve within two weeks after ciprofloxacin was added. Further evidence of the therapeutic effect of ciprofloxacin was demonstrated by the worsening that occurred with ciprofloxacin withdrawal and the improvement that ensued after the drug was reinstated. Since amikacin was not discontinued at any point in the initial treatment, it is not possible to ascertain whether therapy with ciprofloxacin alone would have sufficed in this patient.

Although amikacin remains a mainstay of treatment of atypical mycobacterial keratitis, treatment failures can occur. In these cases, ciprofloxacin therapy may be helpful. Because mutational resistance can develop to single-agent therapy of atypical mycobacterial infections,[5] consideration should be given to combination therapy with amikacin and a fluoroquinolone such as ciprofloxacin. Further clinical and experimental data will be required before final recommendations can be made regarding the role of fluoroquinolones in the first-line therapy of atypical mycobacterial keratitis.

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Aqueous Humor Protein and Intraocular Lens Powers

Lawrence S. Evans, M.D.

Department of Ophthalmology, Stritch School of Medicine.

Inquiries to Lawrence S. Evans, M.D., Department of Ophthalmology, Stritch School of Medicine, Loyola University of Chicago, Maywood, IL 60153.

Theoretical formulas, such as Binkhorst's, to determine the power of an intraocular lens to be implanted after cataract extraction explicitly use the refractive index of the aqueous humor, which is taken to be the constant 1.336.[1] Recently, Jurych and associates[2] have shown that aqueous humor protein may remain increased long after intraocular surgery. They found that the average protein concentration was 40.9 mg/dl in 38 eyes without previous intraocular surgery before cataract extraction. In another group of 50 patients with previous intraocular surgery (an average of 43.9 months previously), the average protein concentration was 100.9 mg/dl. No inflamed eyes or eyes being treated with parasympathomimetic agents were involved in their study. Because protein is a principal solute in aqueous humor, this raises the question of whether such an increase in protein will be sufficient to alter the refractive index of the aqueous humor enough that one should anticipate such changes in selecting the intraocular lens of the appropriate power for implantation. This may be of further interest if the eye to be operated on has had uveitis with subsequent increased aqueous protein.

To determine an estimate of the change in refractive index of the aqueous humor caused by increased protein, I used Sunderman's formula, which demonstrates the linear correlation between refractive index (r.i.) and protein concentration in serum[3]: Protein (g/dl) = 510 × (r.i. serum − r.i. water) − 1.81.

The strong linear relationship between refractive index and serum proteins has been known for over 90 years and has been used clinically to measure serum protein concentrations. Sunderman's relationship is known to hold well in the range of 2,000 to 8,000 mg/dl. However, using Jurych and associates' value of 40.9 mg/dl for aqueous humor protein, Sunderman's formula gives excellent agreement with the usual value of refractive index for the aqueous humor, so it then may be used to estimate the change in refractive index caused by a change in aqueous humor protein concentration. It predicts that the refractive index change will be equal to the change in protein concentration in milligrams per deciliter divided by 510,000. For a change of 60 mg/dl as Jurych and associates have noted, this amounts to an increase of refractive index of only 0.00012. When the new value of refractive index is used in Binkhorst's formula the change in predicted intraocular lens power is only a few thousandths of a diopter, which is not significant. Therefore it appears unnecessary to use an altered value of the refractive index of aqueous humor when determining the power of an intraocular lens.

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Distinguishing Compensatory Head Turn From Gaze Palsy in Children With Unilateral Oculomotor or Abducens Nerve Paresis

William J. Benevento, M.D., and Lawrence Tychsen, M.D.

Department of Ophthalmology and Visual Sciences, Children's Hospital Eye Center, Washington University School of Medicine.

Inquiries to Lawrence Tychsen, M.D., Room 2s89, St. Louis Children's Hospital, Washington University Medical Center, One Children's Place, St. Louis, MO 63110.

The term gaze palsy is sometimes confused in the strabismus literature and has important implications when a surgeon is planning strabismus surgery for unilateral cranial nerve paresis. A gaze palsy is an inability to initiate binocular saccadic or pursuit eye movements to some eccentric orbital position. In the case of a unilateral oculomotor or abducens nerve paresis, a child may adopt a compensatory head

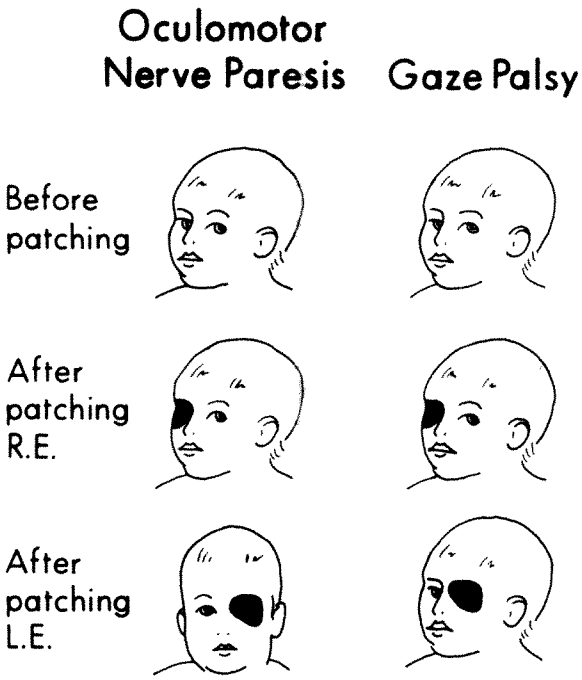


Fig. 1 (Benevento and Tychsen). Patching test for left oculomotor nerve paresis vs right gaze palsy. In oculomotor nerve paresis, patching the paretic eye removes the stimulus for the head turn (attempted binocular fusion) and allows a gradual return of normal extraocular movements in the right eye. In a gaze palsy, patching does not alter the stimulus for the head turn.

turn to achieve binocularity. A strong reluctance to shift gaze out of the zone of binocularity frequently develops, mimicking a gaze palsy. The distinction between a compensatory head turn and a gaze palsy can be crucial in planning strabismus surgery, as illustrated by the following case.

A 5-year-old boy was referred for evaluation of congenital gaze palsy. He strongly preferred to view targets with his head turned to the right, thereby keeping the right eye in the nasal orbit and the left eye in the temporal orbit. Testing of pursuit and saccades under conditions of binocular viewing showed what appeared to be a marked right gaze palsy; the child turned his head, rather than his eyes, whenever a target was presented to his right. Subtle blepharoptosis and iridoplegia of the left eye, with limited supraduction of the left eye, suggested developmental left oculomotor nerve paresis. The parents were instructed to patch the paretic left eye full time. Three days later, eye movements in the right eye were normal, and the head turn had resolved. A left lateral rectus muscle recession, with tendon displacement downward, and left superior oblique muscle tenotomy corrected the exotropia, hypotropia, and head turn. If this case was thought to have represented a gaze palsy, I might have been tempted to recess the medial rectus muscle of the normal right eye to correct its apparent esotropia, the equivalent of a Kestenbaum procedure.[1] Surgery on the normal eye would probably have resulted in postoperative exotropia, as documented in two recent cases of congenital oculomotor nerve palsy.[2]

Patching the paretic eye allows observation for a prolonged inability to initiate eye movements in one direction in the normal eye[3] (Fig. 1). The patching test for gaze palsy is analogous to that used for diagnosing compensatory head tilt in trochlear nerve palsy.[3,4] When viewing binocularly, or monocularly with the paretic

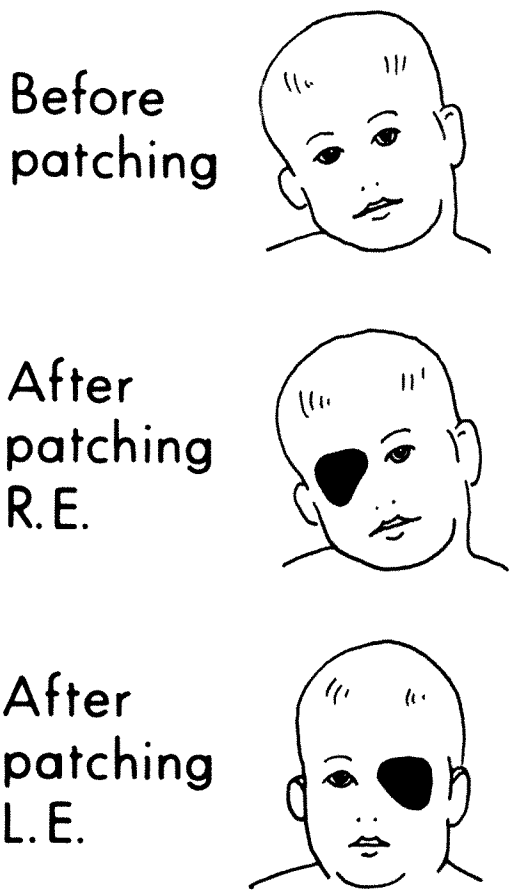


Fig. 2 (Benevento and Tychsen). Patching test for head tilt in left trochlear nerve paresis. Viewing binocularly, the infant has a right head tilt to maintain fusion. Viewing monocularly with the paretic eye, the right head tilt persists. Viewing monocularly with the normal eye, the head tilt resolves.

eye, a child with trochlear nerve paresis displays a compensatory head tilt; however, when viewing monocularly with the normal eye, the child straightens the head (Fig. 2). In an oculomotor or abducens nerve paresis, the paretic eye may need to remain patched for several days before full rotations return to the normal eye and the head turn resolves. This delay corresponds to the amount of time required for recalibration of chronically adapted, normal brainstem gaze neurons.[5]

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Tricholemmal Carcinoma of the Eyelid

John R. Dailey, M.D., Klaus F. Helm, M.D., and Stuart H. Goldberg, M.D.

Departments of Ophthalmology (J.R.D., S.H.G.) and Medicine and Pathology (K.F.H.), Pennsylvania State University College of Medicine. Supported in part by patients and contributors of the Department of Ophthalmology, Penn State University College of Medicine; Research to Prevent Blindness, Inc., New York, New York; and Pennsylvania Lions Vision and Research Center, Hershey, Pennsylvania.

Inquiries to Stuart H. Goldberg, M.D., Department of Ophthalmology, Pennsylvania State University College of Medicine, P.O. Box 850, Hershey, PA 17033.

Tricholemmal carcinoma is a rare cutaneous malignancy that originates in hair sheath. It usually occurs on sun-exposed skin. Fewer than 45 such cases have been reported in the literature to date.[1-4] We treated a patient who had tricholemmal carcinoma on the eyelid.

A 95-year-old woman was referred for evaluation of a left upper eyelid lesion. She had had breast cancer, treated surgically in 1984, and unresectable colon cancer, diagnosed in 1991. One year before our examination, the patient noticed a painless, rapidly growing lesion on her left upper eyelid. The lesion was treated by her primary-care physician with liquid nitrogen on two occasions, which resulted in minimal, temporary regression in the size of the lesion. The patient was referred to us by her ophthalmologist for examination.

Examination disclosed a 14 × 12-mm nodular, crusted, brown lesion of the left upper eyelid (Fig. 1). The lesion was painless, not fixed to underlying tissue, and did not involve the lash line or eyelid margin. Preauricular lymph nodes were not palpable. Clinically, the lesion resembled squamous cell carcinoma or keratoacanthoma. An elliptical excisional biopsy extending to the orbicularis was done. The defect was closed primarily.

Histologic examination showed a tricholemmal carcinoma (Fig. 2). The tumor was composed of lobular sheets of atypical, pale and eosinophilic-staining cells that resembled the outer root sheath of hair follicles extending into the dermis. Focal PAS-positive, diastase-sensitive staining of the pale cells' cytoplasm indicated that they contained glycogen. Additional-



Fig. 1 (Dailey, Helm, and Goldberg). Clinical appearance of tricholemmal carcinoma of the left upper eyelid.

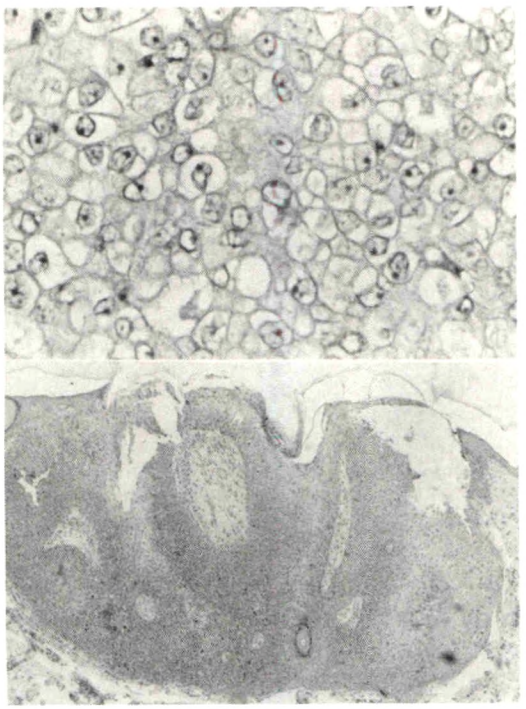


Fig. 2 (Dailey, Helm, and Goldberg). Histologic appearance of tricholemmal carcinoma. Top, The tumor is composed of a mixture of pale and clear cells that resemble the outer root sheath of hair follicles (hematoxylin and eosin, × 500). Bottom, The tumor extends in a lobular arrangement from the epidermis into the upper dermis (hematoxylin and eosin, × 50).

ly, several mitotic figures were noted. The tumor appeared to be centered around hair follicles, and it partially spared the interfollicular epithelium. Pagetoid cells were seen within the epidermis.

Tricholemmal carcinomas are histologically characterized by a follicular-oriented epidermal tumor composed of clear or pale cells that resemble the external root sheath of hair follicles. The tumor may focally involve the interfollicular epidermis, and pagetoid cells may be present. The histologic differential diagnosis includes Bowen's disease (squamous cell carcinoma in situ), clear cell basal cell carcinoma, or sebaceous carcinoma. In these three neoplasms, the histologic findings are not centered around hair follicles. In clear cell basal cell carcinoma, pagetoid cells and involvement of the upper layers of the epidermis should not be present. Sebaceous carcinoma can be excluded by the lack of sebaceous differentiation.

Tricholemmal carcinoma typically occurs on the sun-exposed, hair-bearing skin of elderly individuals. Although occurring most commonly on the scalp and face, in 17 recently reported cases only one case involving the eyelid or ocular adnexa was described.[2-4]

Despite its locally aggressive growth, tricholemmal carcinoma does not appear to metastasize. Local tumor recurrence can occur. Management of tricholemmal carcinoma should include complete surgical excision with histologically documented tumor-free margins, followed by regular clinical examinations. Tricholemmal carcinoma should be considered in the differential diagnosis of eyelid tumors with the appearance of squamous cell carcinoma or keratoacanthoma.

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Correspondence

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Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Meibomian Gland Function and Giant Papillary Conjunctivitis

EDITOR:

In the article "Meibomian gland function and giant papillary conjunctivitis," by W. D. Mathers and M. Billborough (Am. J. Ophthal-

mol. 114:188, August 1992), the authors hypothesized ". . . that meibomian gland dysfunction would cause increased ocular irritation and lead to an increased likelihood of giant papillary conjunctivitis." We believe, however, that the meibomian gland dysfunction could be viewed as a sequela rather than the cause of giant papillary conjunctivitis. There is considerable evidence that giant papillary conjunctivitis is caused by an immunologically mediated response, coupled with contact lens-induced mechanical disturbances. Chronic giant papillary conjunctivitis can lead to immunologically mediated thickening of the lower and upper tarsal conjunctivae. Conjunctival mast cells and a type-1 hypersensitivity reaction play a key role in giant papillary conjunctivitis. Henriquez, Kenyon, and Allansmith[1] found that 30% of conjunctival mast cells are in a state of degranulation in giant papillary conjunctivitis. Furthermore, by immunohistochemical and electronmicroscopic techniques, we demonstrated that the majority of mast cells in giant papillary conjunctivitis are of the connective tissue type on the basis of their neutral protease content.[2,3] We also found increased levels of tryptase, a mast cell specific product and marker in tear samples obtained from patients with giant papillary conjunctivitis. However, tryptase levels were not detected in patients with blepharitis and other nonallergic ocular inflammatory conditions. We believe that in conjunction with infrared meibomian gland photography tryptase assays can be used to evaluate the association between blepharitis and giant papillary conjunctivitis.

SALIM I. BUTRUS, M.D.
ANDREW I. RABINOWITZ, M.D.
Washington, D.C.

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Reply

EDITOR:

Drs. Butrus and Rabinowitz have suggested that meibomian gland dysfunction may be a sequela of giant papillary conjunctivitis rather than the reverse. Inasmuch as we do not know the cause of meibomian gland dysfunction, speculation regarding possible causes is appropriate. We believe that meibomian gland dysfunction may occur as a phenomenon of hyperkeratinization, which occludes the orifice and ducts of the meibomian glands leading to inspissation and gland degeneration. Inflammation of the eyelid margin may be one factor that causes or accelerates this hyperkeratinization process, and giant papillary conjunctivitis with inflammation of the conjunctiva could therefore contribute to the induction of meibomian gland dysfunction. Meibomian gland dysfunction appears, however, to be a process present during most of one's adult life. Conversely, giant papillary conjunctivitis is a relatively short-term phenomenon, and the likelihood that an inflammatory process of the conjunctiva of such a short duration would be a significant cause of this chronic condition of the eyelid margin seems unlikely. Other causes of inflammation of the eyelid margin such as toxins from bacterial flora are more likely candidates. Meibomian duct hyperkeratinization may even be an abnormal response to a normal level of inflammatory stimulus.

None of this reasoning negates the relationship we proposed that meibomian gland dysfunction creates added inflammation, which contributes to giant papillary conjunctivitis.

W. D. MATHERS, M.D.
Iowa City, Iowa
M. BILLBOROUGH, M.D.
West Reading, Pennsylvania

Meibomian Gland Function and Giant Papillary Conjunctivitis

EDITOR:

In the article, "Meibomian gland function and giant papillary conjunctivitis," by W. D.

Mathers and M. Billborough (Am. J. Ophthalmol. 114:188, August 1992), the authors describe an association between giant papillary conjunctivitis and meibomian gland dysfunction blepharitis. On the basis of our clinical impression that these two entities were associated, we initiated a study to test this hypothesis in 1986. We described our results at the 1989 American Academy of Ophthalmology annual meeting[1] and in 1992.[2] This pilot study showed a statistically significant association between the severity of giant papillary conjunctivitis and the severity of meibomian gland dysfunction at initial manifestation in 80 eyes. We were pleased to see that Drs. Mathers and Billborough had similar findings, using meibomoscopy and a new meibomian gland dysfunction classification system. Further research into the area of meibomian gland secretions will likely yield important insights into the pathogenesis of giant papillary conjunctivitis and other immunologically mediated external ocular diseases.

ROY S. RUBINFELD, M.D.
NEIL F. MARTIN, M.D.
Chevy Chase, Maryland

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Clinical and Histopathologic Changes in the Host Cornea After Epikeratoplasty for Keratoconus

EDITOR:

In the article, "Clinical and histopathologic changes in the host cornea after epikeratoplasty for keratoconus," by M. Rodrigues, V. Nirankari, S. Rajagopalan, K. Jones, and J. Funderburgh, (Am. J. Ophthalmol. 114:161, August 1992), the authors point out a major problem with epikeratophakia for keratoconus that might be avoided by alterations in the surgical technique.

First, the extent and severity of the keratoconus cannot really be judged by keratometric readings alone since large cones may be eccentric and corneal topography can be useful in planning surgery.

Second, it is our experience that when the thin ectatic cone material is pushed back, some folds may develop, but in general these disappear and do not impair vision. Conversely, in epikeratophakia as in any lamellar keratoplasty, if the donor tissue is too small in diameter, or is made too small by being pulled into the recipient cornea, it can push back normal-thickness cornea and cause fixed folds in the corneal stroma that produce the problems documented in their article. Our recommended technique for the surgery for keratoconus involves the use of a donor cornea larger in diameter than the recipient bed, since the donor cornea must be laid on top and a larger circumference is required. Additionally, the sutures compress the tissue, so that some additional donor material is required.

In the procedure described in their article, the authors pulled the keratoconus donor tissue under an undermined edge of the annular trephine incision in the recipient cornea. In optical epikeratophakia, we do this undermining and let the edge of the tissue lens slide under the recipient cornea; also, we are careful to suture in such as way that there is no tension to distort the optical lens. In contrast, in the keratoconus corneas, we do not pull the donor tissue under the recipient cornea because the resultant shortening of the effective circumference of the donor produces exactly the problems documented by these authors. Our preferred technique of epikeratophakia for keratoconus involves a vertical trephine incision, no undermining of the peripheral cornea, a 0.5-mm beveled annular keratectomy in the recipient cornea on the inner aspect of the trephination, and apposition of the edge of the donor tissue to the resulting recipient edge. Our present preferred technique is to use a 10-mm-diameter donor cornea and a 9-mm-diameter trephined recipient bed, although sometimes a 9-mm-diameter donor cornea can be used in an 8.5-mm-diameter bed. There is no pulling or tucking of the donor tissue under the recipient cornea.

Theoretically, it would seem that the tighter one pulls the donor cornea, and the smaller the donor tissue, the more the reduction in the

patient's myopia. When carried to extremes, however, the complications described by these authors result. These complications are not inherent in the procedure of epikeratophakia, but rather are related to technique. The residual myopia with the techniques we use is not great, and the recipient folds and glare are minimized. These considerations are not new, but rather have evolved from older studies in which lamellar keratoplasty was used for the treatment of keratoconus, and used with great success.[1-3] Epikeratophakia is nothing more than a lamellar keratoplasty, without the dissection of the recipient bed.

One of the uses of epikeratophakia is illustrated in the authors' Case 3, in which a patient with bilateral keratoconus sustained trauma to an eye in which a penetrating keratoplasty had been performed. The trauma resulted in loss of the lens and necessitated a vitrectomy. The patient was left with 20/25 visual acuity, but this was fortuitous after such a trauma. In the epikeratophakia eye, the preoperative best-corrected visual acuity was described as 20/50 with a hard contact lens, although scarring was not noted. In our experience, this reduction of visual acuity in the absence of any scarring is not seen. In any case, this patient also had trauma to the eye with the epikeratophakia lens; all that resulted in this eye was a partial dehiscence of the graft, which was resutured. Final visual acuity was 20/30. Despite the surgical technique that resulted in some folds, the patient was phakic and without a vitrectomy.

Epikeratophakia, like any surgical procedure, has complications, but some of them, such as some of those illustrated by these authors, are avoidable with modifications in surgical technique.

HERBERT E. KAUFMAN, M.D.
MARGUERITE B. McDONALD, M.D.
New Orleans, Louisiana

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Reply

EDITOR:

We appreciate the interest of Drs. Kaufman and McDonald in our study. While epikeratophakia may be satisfactory in selected cases of keratoconus,[1-5] postsurgical complications have been well documented by several experienced corneal surgeons who followed a standard surgical protocol. These complications have included scarring,[6] corneal steepening,[7] irregular astigmatism,[8,9] interface opacities,[8,9] and multiple folds in Bowman's membrane,[4,8,9] resulting in decreased best-corrected visual acuity. In our study, we found irregular astigmatism, interface opacities, and multiple folds in Bowman's membrane.

Drs. Kaufman and McDonald have pointed out that the use of a donor cornea larger than the recipient bed was important to prevent compression of tissue. We routinely used a 9-mm lenticule and an 8.5-mm recipient bed. The minimal peripheral undermining was done not to pull tissue, but to gently tuck the edge of the lenticule and to provide a smooth surface to facilitate epithelial healing. No keratectomy was done, as we believe that to be an important course of corneal steepening after epikeratoplasty.[7-10]

We agree with Drs. Kaufman and McDonald that the extent and severity of keratoconus cannot be judged by keratometry alone, and that corneal topography can be a useful procedure for early diagnosis and to monitor progression of the disease. However, to date, we are unaware of the existence of any objective standards that use corneal topography and would allow better selection of candidates for epikeratoplasty rather than penetrating keratoplasty.

An important purpose of our study was to demonstrate new histologic and immunohistochemistry changes in the host tissue and lenticules, particularly related to alterations in stromal proteoglycans. Immunostaining of specimens from three cases disclosed a reduced expression of sulfated epitopes of keratan sulfate, and an increase in sulfated dermatan sulfate in the lenticule and host corneal

tissues. These alterations in stromal proteoglycans are characteristic of stromal scars and keratoconus and provide evidence of pathologic processes in the graft tissue.

We believe that with over a 95% long-term success rate for penetrating keratoplasty in keratoconus,[11] the principal advantages of epikeratoplasty, being an extraocular procedure with preservation of host endothelium and avoidance of immunologic rejection, must be balanced against the known risks of other complications and a healing period lasting at least a year.

MERLYN RODRIGUES, M.D.
VERINDER NIRANKARI, M.D.
SANKARAN RAJAGOPALAN, M.D.
KELLY JONES
Baltimore, Maryland
JAMES FUNDERBURGH, M.D.
Manhattan, Kansas

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Visual Outcome After Penetrating Keratoplasty With Double Continuous or Combined Interrupted and Continuous Suture Closure

EDITOR:

In the article, "Visual outcome after penetrating keratoplasty with double continuous or combined interrupted and continuous suture closure," by K. K. Assil, S. R. Zarnegar, and D. J. Schanzlin (Am. J. Ophthalmol. 114:63, July 1992), it is impossible to evaluate the factors of postoperative penetrating keratoplasty, such as keratoscopic astigmatism, refractive cylinder error, and best-corrected visual acuity, until all sutures have been removed. It has been pointed out that there can be large changes in all of these factors when a continuous suture biodegrades or is removed.[1-3] This is also the objection to the adjustable suture as proposed by McNeill and Wessels.[4]

Personally, I prefer to use interrupted sutures and to remove them selectively.[1,2,5]

LOUIS J. GIRARD, M.D.
Houston, Texas

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Reply

EDITOR:

We agree with Dr. Girard that final refractive results can be greatly altered by subsequent suture removal (as stated in the final sentence of our discussion section). We were most interested, however, in assessing the postoperative rate of visual rehabilitation. Furthermore, while the topographic alterations after the removal of continuous sutures may be unpredictable in any given individual, we find that the overall trends in refractive outcome persist after removal of continuous sutures. Additionally, we recently evaluated several different suturing techniques in rabbit studies and by mathematical model analysis. These studies confirmed our observations regarding suture technique-associated alterations in corneal topography. On average, continuous sutures combined with short bites will provide over 7 diopters of central steepening, relative to interrupted closure, employing long suture bites (in particular when long on the recipient side of the wound).

We have found these observations to be useful within our own clinical practice. For an aphakic transplant patient who is a poor candidate for intraocular lens placement, we will provide an oversized graft measuring 1 mm larger than the recipient bed and use double continuous closure, each suture having 12 short bites (achieving over 10 diopters of steepening). Alternatively, in a phakic, severely myopic transplant patient, we use the same size trephine for both the host and recipient bed and either long, interrupted bites or a continuous suture with numerous (18 to 24) long bites to provide a flat cornea.

In addition to the refractive considerations, a significantly greater number of visits were required for the patients receiving interrupted sutures for selective suture removal in order to minimize astigmatism over the course of the study. Furthermore, the average degree of astigmatism within this group still remained markedly greater at one year, compared to the double continuous closure group of patients not requiring subsequent suture manipulation. Within our practice, patients receiving purely interrupted sutures require the greatest number of postoperative visits and retain larger amounts of residual astigmatism after removal of sutures than those receiving other methods of wound closure.

We find that the double continuous closure technique affords the most rapid rate of visual recovery, the smallest degree of postoperative graft astigmatism, and the fewest number of postoperative visits when compared to other techniques of wound closure. The role of the 11-0 continuous suture in achieving these results should not be overlooked. After placing the interrupted 10-0 nylon suture and reforming the eye to physiologic pressure, we used the 11-0 nylon suture to achieve precise approximation of the graft host interface.

Less biodegradable sutures have been found to remain intact for many years postoperatively. Should these sutures achieve greater acceptance, then the specific technique of sutured wound closure will become even more important at the time of penetrating keratoplasty.

K. K. ASSIL, M.D.
S. R. ZARNEGAR, M.D.
D. J. SCHANZLIN, M.D.
St. Louis, Missouri

Vagal Responses to Adjustable Sutures in Strabismus Correction

EDITOR:

In the article, "Vagal responses to adjustable sutures in strabismus correction," by H. S. Eustis, C. S. Eisworth, and D. R. Smith (Am. J. Ophthalmol. 114:307, September 1992), the authors found a much higher incidence of vagal responses during suture adjustment (65%) than I reported with Vrabec and Preslan (4.5%),[1] or was predicted by Flynn.[2] They suggested that possibly our monitoring technique did not detect short vagal responses that may have occurred; however, they also considered that their patients might have truly had a higher incidence of vagal response than ours because of differences in adjustment techniques. I believe the important reasons for the

differences between our two studies can be determined from available data.

Eustis, Eisworth, and Smith suggested that they may have found a higher incidence of vagal responses in part because they monitored blood pressure as well as pulse. Because only one of their patients manifested just a drop in blood pressure as a sign of a vagal response, it is unlikely that our failure to monitor blood pressure was a substantial cause for the differences between our studies. They also suggested that because we used a monitor that averaged pulse over eight seconds, we may have missed brief episodes of bradycardia. They could examine their tracings and see how many of their patients had a bradycardia of 10% or more that lasted less than eight seconds, or a 20% drop that lasted for less than four seconds. This would be important in assessing whether our technique of monitoring may have failed to detect vagal responses that had occurred.

I suspect that the higher incidence of vagal response found by Eustis, Eisworth, and Smith was because of differences in their technique for adjusting sutures. When I began performing adjustable suture surgery in 1976, all of my patients were in-patients and I performed suture adjustment the on morning after surgery. When I switched to out-patient surgery a number of years ago, I initially performed suture adjustments six to eight hours after surgery, and I sensed there was a dramatic increase in clinically apparent vagal responses at the time of adjustment. This prompted me to revert to performing adjustments on the day after surgery in my office, and I observed a drop in the apparent incidence of vagal responses. This seems logical. All inhalation anesthetic agents depress the sinuatrial node and potentiate the vagal reflex; halothane is the worst offender. Inhalation agents are slowly expired from the lungs and are usually present up to 24 hours after surgery.

Only two of the patients described by Eustis, Eisworth, and Smith experienced bradycardia at the time of inserting the eyelid speculum, which does not eliminate the role the eyelid speculum may have played in causing this problem. The authors correctly point out that fear and apprehension contribute to vagal responses. I am convinced that the use of a speculum at the time of adjustment increases the patient's overall sense of anxiety and discomfort. I only use an eyelid speculum in those uncommon patients who have difficulty maintaining downgaze, and in whom I have recessed a superior rectus muscle. Finally, performing suture adjustment with the patient in the upright position seems to increase vagal responses.

The study by Eustis, Eisworth, and Smith provides compelling evidence that the incidence of vagal response at the time of suture adjustment can be decreased by performing the adjustment on the day after surgery, avoiding the use of an eyelid speculum, and possibly having the patient in the supine position.

BURTON J. KUSHNER, M.D.
Madison, Wisconsin

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Reply

EDITOR:

We appreciate Dr. Kushner's thoughtful comments regarding vagal responses when using adjustable sutures. We agree with Dr. Kushner that certain modifications of the adjustable suture method can help in minimizing the incidence of vagal responses. We have independently arrived at similar conclusions, and now use some of the suggestions offered by Dr. Kushner: that is, avoiding the use of an eyelid speculum, and performing the adjustment with the patient in a supine position.

We respect Dr. Kushner's opinion that performing the suture adjustment on the day after surgery further decreases the incidence of vagal responses; however, we would argue that his explanation for this finding is faulty. He states: "Inhalational agents are slowly expired in the lungs and are usually present up to 24 hours after surgery." He reasons that since all anesthetic agents depress the sinuatrial node and potentiate the vagal reflex, suture adjustments the day after surgery should logically

minimize the number of vagal responses. Our anesthesia colleagues advise that these statements are only partly correct. Anesthetic agents do depress the sinuatrial node and potentiate the vagal reflex; however, most inhalational anesthetic agents are quickly expired and not present six hours after surgery. This is especially true for isoflurane and enflurane (agents most commonly used in our study). Halothane, which is absorbed by adipose tissue, may remain in obese patients; however, in most normal individuals it should be completely expired by six hours after surgery.

We suggest an alternate opinion. Many different pharmacologic agents are used in the perioperative period which might have hemodynamic or sinuatrial node consequences in susceptible individuals. These presently unidentified drugs, not anesthetic gases, are the inciting agents. Therefore, we concur with Dr. Kushner that suture adjustments the day after surgery should reduce the incidence of vagal responses as it is more likely that these pharmacologic agents have been cleared. An alternative method for those surgeons who desire adjustment on the day of surgery would be to minimize the preoperative and postoperative medications used, and to use of Propofol, a new intravenously administered anesthetic agent that is rapidly metabolized and has no sinuatrial node activity.

So which incidence figure is correct? We suggest both. The incidence we report is identical to incidence figures in fully anesthetized patients and represents what you could expect on the day of surgery. By using the modifications Dr. Kushner recommends, however, this incidence figure could be reduced to 4.5%. We, therefore, thank Dr. Kushner for his valuable input.

H. S. EUSTIS, M.D.
C. C. EISWORTH, M.D.
New Orleans, Louisiana
D. R. SMITH, M.D.
Toronto, Ontario, Canada

Superior Rectus Muscle Overaction After Cataract Extraction

EDITOR:

I would like to comment on two aspects of the article, "Superior rectus muscle overaction after cataract extraction," by M. R. Grimmett and S. R. Lambert (Am. J. Ophthalmol. 114:72, July 1992).

First, I wonder how consistently we ophthalmologists use certain terms mentioned in the article: overaction, strengthening, and contracture. For good measure, one might also include hypercontraction and hypertrophy. These might be simplified to overaction (to include strengthening and hypercontraction as synonyms and the possible resultant hypertrophy as shown histologically) and contracture.

Although terms such as overaction are often used, I am not sure we have good evidence that it actually occurs in ocular muscles, even though the motility might be consistent with that theory. For example, do we have electromyographic evidence of overaction in these cases?

Although there is some histologic evidence for hypertrophy in strabismus,[1] I am not sure these data confirm contracture. In oculomotor and abducens nerve pareses lasting eight to ten weeks, I do not generally see muscle imbalance. One would think an increasing strabismus over months, muscle tension data showing increased tension in the normal muscle with contracture as the weakened muscle contracts,[2] or biopsy results would be helpful to document contracture.

Secondly, is it possible that in these four cases there was more than one cause for the motility abnormality (for example, additional, subtle trochlear nerve paresis in Case 1 or scarring in more than one orbital location secondary to multiple operations in Case 1)? Could a cause other than overaction, such as scarring in the superior rectus muscle secondary to suture injury, give a condition consistent with theoretic overaction of that muscle?

W. BRUCE WILSON, M.D.
Denver, Colorado

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Reply

EDITOR:

We appreciate Dr. Wilson's interest in our article. We agree with the careful and judicious use of terms describing ocular motility patterns and ocular muscle activity. Confusion can easily occur, depending on whether the practitioner attempts to define terms such as overaction or contracture clinically, histologically, or electromyographically.

Historically, the term overaction has been used to describe a clinical finding: ". . . the affected eye shoots beyond the other in the direction of the field of action of the muscle involved, its movement being quicker and its total excursion greater than that of its fellow."[1] Since this clinical definition is common among practitioners, it is the one we used in our article. Additionally, we are not certain that histologic or electromyographic testing would be necessarily diagnostic because clinical overaction of an ocular muscle can be theoretically secondary to numerous causes: primary neurogenic causes, primary myogenic causes, and secondary myogenic causes.[2] Further study would be required to differentiate the histologic and electromyographic characteristics of each entity.

We applied the term superior rectus muscle contracture to Case 4 where a restriction to depression was found on voluntary levodeorsumduction and was subsequently confirmed on forced duction testing intraoperatively. Although scarring or fibrosis of the superior rectus muscle could hypothetically mimic a finding of restricted levodeorsumduction, it was thought unlikely in Case 4 because direct intraoperative inspection did not disclose marked scarring of the muscle. Hence, we used the clinical term contracture, in agreement with the general definition by O'Connor[3]: "Contracture is present: a) if resistance is felt; b) if the eye cannot be rotated the normal amount by traction." Furthermore, the finding of superior rectus muscle belly enlargement in Case 4 on direct coronal computed tomographic imaging is suggestive of muscle foreshortening or contracture. Unfortunately, a histologic specimen is not available for Case 4.

Dr. Wilson additionally states: "In oculomotor and abducens nerve pareses lasting eight to ten weeks, I do not generally see muscle imbalance." Although the incidence of ocular muscle imbalance from varying degrees of ocular muscle paresis is not precisely known, we refer him to the work of Scott and associates to verify the existence of this clinical entity.[4] Indeed, the basis of botulinum type-A toxin therapy depends on a transient weakness of an ocular muscle with botulinum type-A toxin, which can alter ocular alignment for years even with return of normal innervation to the muscle and return of normal ductions.

Finally, in terms of other possible causes for our described motility disturbance, we are unable to implicate "scarring in the superior rectus muscle secondary to suture injury" or an "additional, subtle trochlear nerve paresis," as suggested by Dr. Wilson. In previous reported cases of superior rectus muscle scarring, the greatest deviation measured was always in deorsumversion.[5] In all cases in our series the patients had the largest vertical deviation in sursumversion, making marked fibrosis or scarring of the superior rectus muscle an unlikely culprit. Furthermore, as mentioned in the article, in Cases 1 through 3 the patients had no restriction of ductions and no scarring identified intraoperatively. Additionally, it is important to note that in Case 3 the patient had no bridle suture or manipulation of the superior rectus muscle at the time of the original operation, making scar tissue formation even more remote in that case. Dr. Wilson's consideration of a right trochlear nerve palsy for Case 1 can be excluded with reasonable certainty because the case does not fulfill the requirements of the three-step test of Parks.[6] Additionally, an excyclotropia was not present by using the double Maddox rod, and versions did not disclose underaction of the right superior oblique muscle or secondary overaction of the right inferior oblique muscle. We certainly would welcome an alternative clinical explanation for the motility pattern observed that matches the clinical findings more exactly than superior rectus muscle overaction.

M. R. GRIMMETT, M.D.
S. R. LAMBERT, M.D.
Atlanta, Georgia

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OPHTHALMIC MINIATURE

From November 1942

Each week in *The Journal of the American Medical Association* there is a long series of obituary notices of deceased doctors. Each notice lists the dead doctor's life attainments. Naturally, some of these notices are long, some of medium length, others short, and it happens that, for reasons of appearance, the printer arranges the notices in order of length—longer ones preceding shorter ones. It occurred to a Brooklyn doctor that this weekly list, thus arranged, might provide an opportunity to determine "what price success" in medicine. So he analyzed 30 such weekly lists and found that the average age of death of the first ten doctors on them was 64.6 years, while the last ten doctors—they who had served faithfully but not gained prominence—lived on to 69.3 years. Thus the price of success proves to be about five years of a doctor's life.

Sci. Am. November 1992, p. 14.

BOOK REVIEWS

Edited by Mark J. Mannis, M.D.

The History of Ophthalmology, vol. 11. The Reform of Ophthalmology, part 1-B, by J. Hirschberg. Translated by F. C. Blodi. Bonn, Germany, J. P. Wayenborgh Verlag, 1992. 425 pages, index, illustrated. $145

The History of Ophthalmology, vol. 11. The Reform of Ophthalmology, part 1-C, by J. Hirschberg. Translated by F. C. Blodi. Bonn, Germany, J. P. Wayenborgh Verlag, 1992. 330 pages, index, illustrated. $145

Reviewed by MARK J. MANNIS
Sacramento, California

The newest volumes of this monumental translation undertaken by Dr. Blodi deal with the period Hirschberg terms the "reform of ophthalmology." Hirschberg's work in translation is not a smooth-reading narrative but rather a scholarly treatise with short, numbered sections of documentary of the personalities and development of ophthalmology in the 19th century.

In these two volumes, the method of historical reconstruction is biographically based. A glance at the table of contents discloses a list of great names of European ophthalmology that live on in eponymic fame: Graefe, Schirmer, Groenouw, Axenfeld, Vossius, Arlt, Elschnig, and many others. What makes these two volumes very special is that Hirschberg was personally acquainted with most of the subjects of his history during this period. Accordingly, in addition to the documentation of their training, accomplishments, and contributions to the ophthalmic literature, the reader is treated to Hirschberg's personal assessment of their personalities and capabilities. For example, Hirschberg describes one colleague as "a slender man with black curly hair . . . thought to be handsome, [but] he was neither a scholarly physician nor a well-trained physician." The added dimension of personal acquaintance adds a special touch to the account and, as such, makes this history a personal reflection of the historian's own biases. Hirschberg also reviews his own professional career and contributions, indicating that he ceased practicing clinical ophthalmology in 1907 to dedicate himself to the completion of his history of ophthalmology.

Together with the professional biography of each ophthalmologic luminary, Hirschberg includes a list of his publications. The reader cannot help but muse over the breadth of interest and capability of individuals like Arthur von Hippel whose publications included such diverse areas as studies of intraocular pressure, color blindness, tuberculin treatment, myopia, and the development of a new corneal trephine. The account reflects an era when much of clinical ophthalmology was still new territory and when the ophthalmologist was much less compartmentalized in his thinking.

These volumes are prepared in a format identical to that of the preceding volumes of this publication, and they include beautiful glossy photographic reproductions of the major historical personalities discussed. The books are marred only by the often amusing but unforgivable typographical errors and misspellings that should not be part of this magnificent series. Sadly, the first of these occurs on the dedication page of these two volumes.

Hirschberg was an indefatigable historian. The previous volumes have reflected his scholarship and thorough acquaintance with our profession from its inception. These two volumes give us even greater insight into the development of modern ophthalmology during a critical period of its formative years in Europe. Hirschberg's personal role in this era gives the account a special appeal.

Pondering Hirschberg's panoramic history of ophthalmology provided to the English-speaking world by Dr. Blodi, one wonders who will be our own historian? Hirschberg ends his history spanning 2,000 years with the following words: "Every physician who seriously concerns himself with ophthalmology will have a wide and grateful field of humane activities. The most important message of the 19th century for the 20th is an even better education and training of physicians in the field of ophthalmology. The . . . enormous work which has been accomplished by ophthalmology . . . was achieved for the progress of science and for the benefit of mankind."

We can only hope that as the 20th century

comes to a close, our own chronicler will be able to say that we heeded the message of the 19th century and that the legacy of present-day ophthalmology is as rich as the one we received.

Age-Related Macular Degeneration. Principles and Practice. Edited by G. Robert Hampton and Philip T. Nelson. New York, Raven Press, 1992. 316 pages, index, illustrated. $80

Reviewed by THOMAS G. CHU
Sacramento, California

Age-related macular degeneration is a major cause of visual debilitation. Our management of this disorder, from a preventive and therapeutic standpoint, still is limited. This book attempts to bring together under one cover the current state of knowledge of age-related macular degeneration.

As alluded to in the preface by the editors, this book is primarily written for the general ophthalmologist and the ophthalmologist-in-training. It is divided into 12 chapters, comprising the epidemiologic and pathophysiologic aspects of age-related macular degeneration, the diagnosis of age-related macular degeneration, therapeutic management, and ancillary services and resources available to the patient with age-related macular degeneration. In general, the text is well organized and written, containing valuable information helpful to the general ophthalmologist interested in learning more about age-related macular degeneration. The photographs included in the chapter on the clinical manifestations of age-related macular degeneration are particularly illustrative. Furthermore, the chapter on resources for patients with age-related macular degeneration also provides a useful listing of services available to afflicted patients.

The book, is uneven, however. Whereas many of the chapters are detailed and comprehensive, others are too general. In particular, I found the chapters on office examination and fund photography to be superfluous. The chapter on office examination stresses thoroughness in history taking and examination, which should be self-evident to the practicing ophthalmologist. The chapter on fundus photography and angiography is written primarily with the technician in mind rather than the physician.

Overall, this book does manage to accomplish what was set forth in its preface, to educate the general ophthalmologist and ophthalmology resident about this difficult disease. It is not, nor was it intended to be, a definitive text on the subject. Despite minor limitations, it does manage to provide a good review for the ophthalmologist desiring to learn more about this subject.

Adler's Physiology of the Eye, ed. 9. Edited by William M. Hart, Jr. St. Louis, Missouri, Mosby Year Book, Inc., 1992. 888 pages, index, illustrated. $82

Reviewed by WILLIAM GRUZENSKY
Sacramento, California

Together with advances in research in ocular physiology there is the need to access this information in an efficient manner. Adler's Physiology of the Eye has been a valuable resource in meeting this need since the publication of the first edition in 1950. Although hundreds of pages of scientific research are published almost weekly, truly revolutionary changes in our understanding of ocular physiology occur only gradually as bits and pieces of new information are woven into a composite whole. The role of Adler's Physiology of the Eye has been to synthesize such a composite from both established and contemporary work. William Hart and his contributing authors have produced an updated edition of this authoritative text.

The book attempts to cover the entire spectrum of basic knowledge about the anatomy, biochemistry, physics, pharmacology, electrophysiology, and psychophysics of the eye and visual system. Detailed descriptions of the results of basic research in ocular physiology are given along with extensive references. The text is supplemented with illustrations, graphs, and diagrams, as well as light and electron micrographs. The discussions tend to be comprehensive without particular regard to clinical relevance. However, clinical correlates are often given to enhance the coverage of appropriate topics.

Readers of previous editions of Adler's Physiology of the Eye will find much that is familiar in the new edition. Several notable changes have been made, however. The chapter on vit-

reous anatomy and physiology has been extensively updated in light of recent advances in techniques used for its study. The most significant additions to this chapter are dramatic photographs of vitreous fibrillar structure taken with dark-field slit-lamp illumination. The chapter on biochemistry of photoreceptor sensory transduction has been extensively revised and rewritten. One notable advance in this field is the application of genetic cloning techniques to the study of cone visual pigments. The mechanisms of photoreceptor function and light adaptation have been further elucidated. Chapters on the cornea, lacrimal system, retina, and optic nerve have been rewritten and extensively revised. Newly rewritten chapters cover the subjects of intraocular pressure, color vision, binocular vision and accommodation, and the central visual pathways. References have been updated and expanded.

A compendium of information as extensive as Adler's Physiology of the Eye, no mater how well compiled and edited, would be virtually useless without a good indexing system. This need has been addressed in the new edition with a vast expansion and a dramatic change in the method of indexing. The list of major keywords has been nearly tripled. Part of the expansion can be accounted for by the inclusion of the names of cited authors in the index. Another helpful feature is the addition of references to animal research under the animal species name (for example, "Rabbit eye" and "Raccoon, accommodation ability"). Overall, I think the improved index will make this text a more useful reference.

An attempt to cover such a vast body of information in a single text requires the input of many contributors. This requirement leads to one shortcoming of the book. Contributors bring to their sections a variety of writing styles and goals. Some authors attempt to produce readable material with a maximum of clinically relevant information. At times this may be done at the expense of detailed, comprehensive coverage of the subject. For example, the theme of the newly rewritten chapter on the lacrimal apparatus is correlation of structure and function with clinical abnormalities of tear production and drainage. This is in sharp contrast to the encyclopaedic coverage of the oculomotor system in which clinical correlation is sacrificed in favor of completeness.

Despite this uneveness, the book fulfills its intended purpose well. It is not likely to captivate the casual reader, but researcher and clinician alike will find in it a gold mine of useful information.

Books Received

Ophthalmic Toxicology (Target Organ Toxicology Series). Edited by George C. Y. Chiou. New York, New York, Raven Press, 1992. 328 pages, index, illustrated. $110

This is a well-annotated collection that deals with virtually every aspect of ocular toxicology. It will be of particular interest to the researcher active in finding new additions to the ophthalmic pharmacopoeia. Beginning with an interesting chapter on the history of ophthalmic pharmacology, the book includes chapters on the toxic responses of specific ocular tissues, species specific toxicology, in vivo and in vitro testing methods, ophthalmic toxicity by local and systemic drugs, air pollution and toxicity, occupational hazards and ocular toxicity, and the treatment of chemical ocular injury. The excellent subject index is particularly useful, making this a fine reference for the clinician as well.

Ophthalmology Oral History Series. A Link with our Past. An Interview with Paul Boeder. Interviewed by Sally Smith Hughes. San Francisco, American Academy of Ophthalmology, 1992. 194 pages, index, illustrated. $35

This is the most recent addition to the Oral History Series initiated by the American Academy of Ophthalmology in 1986. Like the previous volumes, the newest on Paul Boeder, Ph.D., is a series of interviews preserving the recollections and role of Dr. Boeder in the development of 20th century American ophthalmology. Recorded in an informal interview style, the book contains insights into the academic life of Dr. Boeder, whose impact on the teaching of visual optics in this country was pervasive. The reader will learn not only about Dr. Boeder's distinguished career in physiologic optics, but will also get a uniquely personal glimpse of the individuals and events that contributed to the

development of present-day ophthalmology. Other volumes in the Oral History Series include interviews with Dohrmann Pischel, Phillips Thygeson, Harold Scheie, Thomas Duane, and David Cogan.

Pediatric and Adolescent Endocrinology, vol. 22. Structural and Functional Abnormalities in Subclinical Diabetic Angiopathy. Edited by B. Weber, W. Burger, and T. Danne. Basel, Switzerland, Karger, 1992. 242 pages, index, illustrated. $196

This is a compilation of the invited lectures and free papers presented at the Third International Workshop on Diabetic Angiopathy in Children, held in Berlin in 1991. It is divided into three sections: basic mechanisms, diagnostic procedures, and therapeutic interventions. The book will be of particular interest to individuals involved in research in or the management of diabetic angiopathy in the pediatric patient. It is perhaps of greater interest to the pediatric endocrinologist. However, there are papers on diabetic retinopathy that describe the relationship between puberty and the development of nonproliferative retinopathy as well as the effect of normoglycemia on retinopathy in insulin-dependent diabetes.

OPHTHALMIC MINIATURE

The only thing she retained of her depravity and degeneracy was her false eye, which would slide out of its orbit during some awkward movements and pop out onto her cheek like a soft-boiled egg. This must have been an awful sight, but Andrei made a fuss over it, drove Nadya, who held her eye in her hand, to the hospital, and there they set the eye back in, and on those nights, I think, Andrei had his supreme moments.

Helena Goscilo and Byron Lindsey (eds.), *Glasnost: An Anthology of Russian Literature Under Gorbachev*
Ann Arbor, Ardis Publishers, 1990, p. 7

ABSTRACT DEPARTMENT

Edited by George B. Bartley, M.D.

Calculating the surgically induced refractive change following ocular surgery. Holladay, J. T.*, Cravy, T. V., and Koch, D. D.: J. Cataract Refract. Surg. 18:429, 1992.

Several formulas have been developed to calculate corneal astigmatism after keratorefractive procedures, cataract extraction, or penetrating keratoplasty. Although each formula has unique merits, all of the calculations "represent gross simplifications of the complex topographical changes that occur on the aspheric corneal surface." To encourage a standardized determination of surgically induced spherical and astigmatic changes, the authors proposed a ten-step method that is based on the oblique cross-cylinder solution. Additionally, several applications of the formula were illustrated, including the addition of the overrefraction to the spectacle correction, the determination of the surgically induced refractive change from the preoperative and postoperative refraction results or keratometry measurements, the effect of rotating axes, the determination of the power at meridians oblique to the principal spherocylindrical meridians, the calculation of the changes in power that occur in the surgical meridian and the meridian 90 degrees away (the coupling ratio), and the averaging of cylinder axes.—George B. Bartley

*Hermann Eye Center, 6411 Fannin, Houston, TX 77030.

Outcome of treatment for bilateral congenital cataracts. Robb, R. M.*, and Petersen, R. A.: Ophthalmic Surg. 23:650, 1992.

The outcome of treatment for bilateral congenital cataracts was studied retrospectively in a group of 51 patients. Two major categories of lens opacities were identified. In the first category, the opacities were extensive and visual impairment was evident early in the first year. These cataracts often occurred in eyes with small corneal diameters and poorly dilating pupils. Postoperative strabismus was nearly universal; nystagmus developed in over 50%; and late onset open-angle glaucoma developed in 8 of the 29 patients studied. Early surgery did not seem to abort the development of nystagmus in this group of patients. In the second category, the lens opacities were partial, often lamellar in configuration, and visual impairment was less severe. Surgery was usually performed after 3 years of age, with good visual results if the opacities were symmetrical and there was no nystagmus. No deprivation amblyopia developed in this group, even when surgery was delayed into the second decade. Strabismus developed postoperatively in about a third, but so far, no delayed open-angle glaucoma has been identified.—Authors' abstract

*Department of Ophthalmology, Children's Hospital, 300 Longwood Ave., Boston, MA 02115.

Posterior capsule opacification. Apple, D. J.*, Solomon, K. D., Tetz, M. R., Assia, E. I., Holland, E. Y., Legler, U. F. C., Tsai, J. C., Castaneda, V. E., Hoggatt, J. P., and Kostick, A. M. P.: Surv. Ophthalmol. 37:73, 1992.

A complication of extracapsular cataract extraction with or without posterior chamber intraocular lens (PC-IOL) implantation is posterior capsule opacification. This condition is usually secondary to a proliferation and migration of residual lens epithelial cells. Opacification may be reduced by atraumatic surgery and thorough cortical clean-up. Clinical, pathological, and experimental studies have shown that use of hydrodissection, the continuous curvilinear capsulorhexis and specific IOL designs may help reduce the incidence of this complication. Capsular-fixated, one-piece all-polymethylmethacrylate PC-IOLs with a C-shaped loop configuration and a posterior convexity of the optic are effective. Polymethylmethacrylate loops that retain "memory" create a symmetric, radial stretch on the posterior capsule after in-the-bag placement, leading to a more complete contact between the posterior surface of the IOL optic and the taut capsule. This may help form a barrier against central migration of epithelial cells into the visual axis. Various pharmacological and immunological methods are being investigated but conclusive data on

these modalities are not yet available.—Authors' abstract

*Department of Ophthalmology, Medical University of South Carolina, 171 Ashley Ave., Charleston, SC 29425.

Intravenous sedation for ocular surgery under local anaesthesia. Salmon, J. F.*, Mets, B., James, M. F. M., and Murray, A. D. N.: Br. J. Ophthalmol. 76:598, 1992.

Forty-nine patients undergoing anterior segment operations were treated two hours preoperatively with 10 mg of temazepam and 10 mg of metoclopramide orally, and then were assigned randomly to receive intraoperatively no sedation, a continuous infusion of propofol (average total dose, 43.2 mg), or a continuous infusion of midazolam (average total dose, 1.41 mg). A peribulbar block containing bupivacaine, lidocaine, and hyaluronidase was administered to each patient. There were no marked differences between the three groups regarding systolic blood pressure, heart rate, respiratory rate, snoring, minimum oxygen saturation, maximum end tidal pressure of carbon dioxide, or postoperative pain, nausea, headaches, or dreaming. Although unexpected patient movement was more frequent in patients who received intravenous sedation, movement of the operative field was not significantly ($P > .05$) affected. The authors concluded that "continuous intravenous sedation with propofol or midazolam is not beneficial in well prepared and informed patients who have received a simple premedication of temazepam and metoclopramide. . . the ideal patient undergoing ophthalmic surgery is conscious, cooperative, and pain free."—George B. Bartley

*Department of Ophthalmology, Medical School, University of Cape Town, Observatory, Cape Town, South Africa.

Is atopy a risk factor for the use of contact lenses? Kari, O.*, and Haahtela, T.: Allergy 47:295, 1992.

In Finland, where 20% to 30% of young people have been reported to have a predisposition to atopy, individuals who wish to use contact lenses are required to undergo an ophthalmic examination. In this study, the authors studied 76 patients for whom daily-wear soft contact lenses were being dispensed for the first time. Sixty-four of the subjects were women, the average age of the patients was 20 years, and the mean follow-up interval was 1.7 years. Twenty-four patients had a history of atopy (seasonal hay fever, perennial rhinitis, urticaria, or nonfacial eczema). A conjunctival scraping for cytologic analysis was performed for each patient as part of the initial examination. Fourteen of the 24 atopic patients (58%) had symptoms (foreign-body sensation, erythema, itching, pain, or lacrimation) related to contact lens wear, compared with 17 of the 52 subjects without a history of atopy ($P < .05$). The risk of experiencing untoward symptoms while wearing contact lenses was calculated as being five times higher in atopic patients than in subjects without atopy. Additionally, the cytologic detection of eosinophils or neutrophils appeared to predict poor tolerance of contact lenses. The authors concluded that patients with a history of atopy should restrict their use of contact lenses during seasonal allergies.—George B. Bartley

*Department of Allergic Diseases, Helsinki University Central Hospital, Meilahdentie 2, 00250 Helsinki, Finland.

Cyclosporine A for the treatment of necrotizing scleritis and corneal melting in patients with rheumatoid arthritis. McCarthy, J. M., Dubord, P. J., Chalmers, A.*, Kassen, B. O., and Rangno, K. K.: J. Rheumatol. 19:1358, 1992.

Necrotizing scleritis and keratolysis are uncommon but potentially devastating complications of rheumatoid arthritis. The authors treated six patients with severe necrotizing disease that had failed to respond to topical lubrication, high-dose oral or intravenous corticosteroids, and pulse cyclophosphamide. Five patients had scleritis and one patient had severe corneal thinning. Cyclosporine was administered at an initial dose of 2.5 mg/kg of body weight per day with subsequent dosage adjustments to maintain trough whole blood levels between

150 and 200 ng/ml. Additionally, all patients were treated with a three-day course of methylprednisolone (1,000 mg intravenously per day), followed by maintenance doses of prednisone (60 to 80 mg daily). Renal function deteriorated in each patient to varying degrees and precluded optimal cyclosporine therapy in one patient. During an average follow-up interval of 38 months (range, four to 66 months), ocular and rheumatoid signs and symptoms improved markedly in the five patients who satisfactorily tolerated cyclosporine. Serum creatinine and urea levels returned to or toward normal after the discontinuation of cyclosporine. Noncorticosteroidal anti-inflammatory drugs may potentiate cyclosporine-induced renal dysfunction, however, so concomitant therapy should be avoided.—George B. Bartley

*Department of Medicine, Vancouver General Hospital, 855 W. 12th Ave., Vancouver, B.C., Canada V5Z 1N9.

Renal function and blood pressure in patients receiving long-term, low-dose cyclosporine therapy for idiopathic autoimmune uveitis. Deray, G.*, Benhmida, M., Hoang, P. L., Maksud, P., Aupetit, B., Baumelou, A., and Jacobs, C.: Ann. Intern. Med. 117:578, 1992.

The authors studied 16 patients with idiopathic autoimmune uveitis who were normotensive and had normal renal function before treatment with long-term, low-dose cyclosporine to determine the renal side effects of the drug. The initial dosage of cyclosporine was 5 mg/kg of body weight per day. After two years of treatment, the serum creatinine level increased by 0.40 ± 0.06 mg/dl ($P < .01$), the creatinine clearance decreased from 120 ± 5 ml/min to 75 ± 4 ml/min ($P < .01$), the glomerular filtration rate decreased from 116 ± 8 ml/min to 75 ± 3 ml/min ($P < .05$), and effective renal plasma flow decreased from 455 ± 24 ml/min to 338 ± 30 ml/min ($P < .05$). Additionally, statistically significant ($P < .05$) increases in serum levels of uric acid, total cholesterol, and potassium were measured at various times during treatment. Hypertension developed in 13 of the 16 patients (81%); in all but two patients, blood pressure was controlled with a beta-adrenergic blocking agent. The authors concluded that long-term cyclosporine therapy, even at a low dose in patients with healthy native kidneys, is nephrotoxic and is associated with a high incidence of hypertension.—George B. Bartley

*Service de Néphrologie, Hôpital de la Pitié, 83 boulevard de l'Hôpital, 75013 Paris, France.

Screening for fungal endophthalmitis in children at risk. Enzenauer, R. W.*, Calderwood, S., Levin, A. V., Elder, J. E., and Morin, J. D.: Pediatrics 90:451, 1992.

Ophthalmoscopy with pupillary dilation is routinely performed at many hospitals in patients with unexplained fever who are at high risk for opportunistic infections. At the authors' institution, children with cancer, in whom fungal infections pose serious potential risks for morbidity and mortality, constitute the largest proportion of such patients. The authors reviewed the medical records of 176 children to determine the efficacy of screening ophthalmic examinations. The patients were divided into the following groups: group 1 (47 patients), those with deep-tissue fungal infection; group 2a (48 patients), those with a positive fungal culture for superficial colonization; and group 2b (81 patients), those with a negative fungal culture. Of the seven patients who had endogenous fungal endophthalmitis, six were in group 1 and one was in group 2a. The risk of endogenous fungal endophthalmitis was at least 19 times greater for patients with deep-tissue fungal infection (group 1) than for patients who were "at risk" (groups 2a and 2b). The risk of endophthalmitis in group 1 patients was at least seven times that of patients in group 2a and 12 times that of group 2b patients. The authors concluded that ophthalmoscopy with pupillary dilation is necessary for patients with invasive fungal disease and is useful for at-risk patients with superficial fungal colonization, but that such examinations are not of documented value in at-risk children with negative fungal cultures.—George B. Bartley

*Department of Ophthalmology, Fitzsimons A.M.C., P.O. Box 6228, Aurora, CO 80045.

Phenotype-genotype correlations in X linked retinitis pigmentosa. Kaplan, J.*, Pelet, A., Martin, C., Delrieu, O., Aymé, S., Bonneau, D., Briard, M. L., Hanauer, A., Larget-Piet, L., Lefrançois, P., Michel-Awad, A., Plauchu, H., Dufier, J. L., Frézal, J., and Munnich, A.: J. Med. Genet. 29:615, 1992.

Retinitis pigmentosa is a progressive degenerative disorder in which all modes of inheritance have been described. Two distinct clinical patterns of X-linked retinitis pigmentosa have been identified. The first form is characterized by the early onset (mean age, 3.5 years) of severe myopia, whereas the second subtype manifests initially with night blindness at an average age of 10.6 years. No difference in either disease severity or fundus appearance is observed between the two profiles in adulthood: both types lead to total night blindness, severe visual field constriction after 15 years of age, and markedly decreased visual acuity after 25 years of age. Although two gene loci previously had been identified for X-linked retinitis pigmentosa, correlation with the two clinical phenotypes had not been accomplished. In this study, the authors provided evidence for linkage of the two clinical subtypes with the RP2 and RP3 genes on the short arm of the X chromosome.—George B. Bartley

*Unité de Recherches sur les Handicaps Génétiques de l'Enfant, INSERM U12, Hôpital des Enfants Malades, 149 rue de Sèvres, 75743 Paris Cedex 15, France.

Human retinal pigment epithelial cells possess β_2-adrenergic receptors. Tran, V. T.*: Exp. Eye Res. 55:413, 1992.

The author studied the binding of [^{125}I]cyanopindolol to cultured human retinal pigment epithelium and calculated that there are 14,000 β-adrenergic receptor sites per retinal pigment epithelial cell. The receptor sites are more likely to be β_2 rather than β_1 for the following reasons: (1) the rank order of potency of agonists for the displacement of cyanopindolol binding was isoproterenol > epinephrine > norepinephrine, and (2) the β_2-specific antagonist ICI-118551 was more potent than the β_1-selective antagonist betaxolol in competing for the specific binding of cyanopindolol. As in other cells and tissues, the β_2-receptors on human retinal pigment epithelium are coupled to adenylate cyclase. The author postulated that the receptors may affect transepithelial fluid movement across the retinal pigment epithelium and Bruch's membrane. Two potential clinical applications were discussed. First, a β_2-adrenergic mechanism may contribute to the pathogenesis of central serous chorioretinopathy if affected patients have higher circulating levels of catecholamines, as has been inferred. Second, systemic medications that interact with β_2-adrenergic receptors, such as some antihypertension drugs or antiasthma agents, may potentially affect the ability of the retinal pigment epithelium to metabolize and phagocytose rod outer segment membranes that are shed.—George B. Bartley

*Department of Ophthalmology, University of Southern California School of Medicine, Los Angeles, CA 90033.

Human eye. Visualization of perfluorodecalin with F-19 MR imaging. Gewiese, B. K. O.*, Noske, W., Schilling, A. M., Stiller, D. A., Wolf, K.-J., and Foerster, M. H.: Radiology 185:131, 1992.

The authors described an 11-year-old patient who underwent pars plana vitrectomy, membranectomy, and retinal detachment repair with perfluorodecalin. Although postoperatively the view of the fundus was obscured by a small pupil, intraocular gas bubbles, and an anterior chamber hemorrhage, it was suspected that residual perfluorodecalin was present after it had been drained and replaced by air and 40% sulfur hexafluoride. Fluorine-19 magnetic resonance imaging was used to confirm the presence and location of perfluorodecalin, which facilitated its removal. Although fluorine-19 magnetic resonance imaging previously had been used in animal experiments, this case was apparently its first application in humans. Any magnetic resonance imager equipped with a fluorine channel can be used to perform this technique, without chemical shift-selective excitation or detection.—George B. Bartley

*Elberfelder Strasse 35, 1000 Berlin 21, Germany.

Comparison of transcutaneous incisions used for exposure of the infraorbital rim and orbital floor. A retrospective study. Bähr, W.*, Bagambisa, F. B., Schlegel, G., and Schilli, W.: Plast. Reconstr. Surg. 90:585, 1992.

Surgical exposure of the inferior portion of the orbit may be achieved by either a transconjunctival or a transcutaneous incision. The transconjunctival route has the advantage of avoiding a skin scar but has the disadvantage of limited exposure. A cutaneous incision may be complicated by postoperative scleral show, ectropion, persistent eyelid edema, or an aesthetically unacceptable scar. The authors studied 105 patients who underwent surgical exploration of the inferior orbital floor through one of three skin incisions to compare the incidence of long-term complications. The three surgical approaches were as follows: (1) subcilial (2 mm inferior to the lower eyelid lashes), (2) subtarsal (parallel to the eyelid margin, at the level of the inferior tarsal border), or (3) infraorbital (in a skin crease at the level of the inferior orbital rim). Subcilial incisions were associated with the highest frequency of scleral show and ectropion but had a low incidence of noticeable scars or edema. Infraorbital incisions, in contrast, caused no ectropion, but they were associated with the highest frequency of visible scars and eyelid edema. Complications that were present six months postoperatively were unlikely to improve spontaneously thereafter. The authors concluded that the subtarsal lower eyelid incision is the preferred route for exposure of the inferior portion of the orbit.—George B. Bartley

*Department of Oral and Maxillofacial Surgery, University Hospital, Hugstetterstrasse 55, W-78 Freiburg, Germany.

Eyelid level after lower lid blepharoplasty with skin excision. The relationship of intraoperative and postoperative lid levels. Becker, B. B.*, and Berry, F. D.: Arch. Otolaryngol. Head Neck Surg. 118:959, 1992.

Lower eyelid blepharoplasty may be complicated by postoperative eyelid retraction ("scleral show"). Several intraoperative techniques, such as asking the patient to look superiorly or to open the mouth widely, have been suggested to help the surgeon determine the appropriate amount of skin to excise. The authors compared the postoperative eyelid positions in 67 patients (134 eyelids) to standardized preoperative and intraoperative photographs. A direct correlation was found in 119 eyelids (89%). Nine eyelids that were normally positioned intraoperatively were retracted postoperatively; in each instance the preoperative photograph documented preexisting eyelid retraction. Of 22 eyelids with intraoperative retraction, 16 (73%) were retracted postoperatively and six (27%) were normally positioned. The authors recommended that skin excision be performed cautiously or avoided in patients with preoperative inferior scleral show. Additionally, horizontal lower eyelid shortening procedures should be done in conjunction with blepharoplasty (as was done in 52 of the 67 patients in this series) if horizontal eyelid laxity or lower eyelid retraction are present preoperatively.—George B. Bartley

*5363 Balboa Blvd., Suite 246, Encino, CA 91316.

Cutaneous micrographic surgery. Mohs procedure. Miller, P. K., Roenigk, R. K.*, Brodland, D. G., and Randle, H. W.: Mayo Clin. Proc. 67:971, 1992.

Cutaneous micrographic surgery, also known as Mohs excision, differs from standard frozen-section examination of surgical specimens in that 100% of the tissue margin is inspected. The technique yields high cure rates for skin cancers and is particularly useful in the treatment of recurrent tumors, lesions that are histologically aggressive (such as morpheaform, metatypical, or micronodular basal cell carcinomas), or tumors that develop in "high-risk sites" (including the eyelids and medial canthus). The authors treated 3,355 skin tumors in 2,265 patients between July 29, 1986, and June 30, 1991. The most common neoplasms were basal cell carcinomas (2,614 basal cell carcinomas; 77.9%) and squamous cell carcinomas (711 squamous cell carcinomas; 21.2%). Of the 3,241 tumors that developed in the skin of the head and neck, 285 involved the eyelids (282 basal cell carcinomas, two squamous cell carcinomas, and one unspecified tumor). Five of the eyelid cancers recurred, yielding an overall cure rate of 98.2%. The authors acknowledged, however, that comparison with cure rates from

previously published reports is not appropriate until a minimum follow-up of at least five years is available for all cases. Excisional defects were usually repaired with simple closure by dermatologists or were allowed to heal by secondary intention; healing by secondary intention is particularly useful for lesions in the medial canthal region. Extensive or complicated defects were reconstructed by specialists in other disciplines. An analysis of Medicare fees demonstrated that Mohs excision was cost-effective in comparison with hospital outpatient surgical excision or radiation therapy.—George B. Bartley

*Department of Dermatology, Mayo Clinic, Rochester, MN 55905.

Lack of protective immunity against reinfection with hepatitis C virus. Farci, P.*, Alter, H. J., Govindarajan, S., Wong, D. C., Engle, R., Lesniewski, R. R., Mushahwar, I. K., Desai, S. M., Miller, R. H., Ogata, N., and Purcell, R. H.: Science 258:135, 1992.

Although non-A, non-B hepatitis has been recognized since the 1970s, it has been established only in the past few years that hepatitis C virus is the principal cause of the infection. Hepatitis C virus is responsible for more than 90% of cases of posttransfusion hepatitis in the United States and results in chronic infection in most patients. Some individuals infected with hepatitis C virus have multiple episodes of acute hepatitis, and it has been unclear whether recrudescences represent reinfection with hepatitis C virus or reactivation of the original virus. To investigate this question, five chimpanzees were sequentially inoculated over a period of three years with different hepatitis C viral strains. Each rechallenge with the same or a different strain caused the reappearance of viremia that correlated with the subsequent challenge virus. The authors concluded that infection with hepatitis C virus does not elicit or confer protective immunity against reinfection with homologous or heterologous viral strains. It was postulated that the virus fails to induce an appropriate neutralizing antibody response or that genetic variation allows the rapid emergence of escape mutants that circumvent the immune response. In either case, the development of effective vaccines against hepatitis C virus may prove to be difficult.—George B. Bartley

*Hepatitis Viruses Section, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892.

Health care reform. Fein, R.*: Sci. Am. 267(5):46, 1992.

Health care absorbed $4 billion (4% of the United States' gross national product) in 1940, in contrast to an estimated $800 billion (13.4% of gross national product) in 1992. Despite this expenditure, an estimated 35 million Americans have no health insurance and many others have only limited coverage. The author, who is a professor of the economics of medicine, reviewed the development of health insurance after the conclusion of World War II, discussed the reasons for and the implications of the escalation of health care costs, compared health care expenditures of several member nations of the Organization for Economic Cooperation and Development, and concluded that "the development of a novel health care system is ethically and economically imperative." A single universal health insurance program, to be administered by the states rather than the federal government, was proposed. The author believes that such a system would be more efficient than "pay-or-play" plans that would require a business either to pay a specified amount to a government insurance fund or to provide its employees with health insurance that meets a predetermined benefit standard. The author conceded that his program may result in "the possible need for rationing" of health care, but it would substitute "an equitable rationing scheme for the price-rationing system that now exists." This article is a succinct summary of the historical background that underlies current debates about health care reform.—George B. Bartley

*Harvard Medical School, 25 Shattuck, Boston, MA 02215.

Cardiopulmonary resuscitation. Niemann, J. T.*: N. Engl. J. Med. 327:1075, 1992.

Cardiopulmonary arrest, defined as "the abrupt cessation of spontaneous and effective

ventilation and systemic perfusion," usually results from a cardiac arrhythmia. A cardiac arrest in a hospitalized patient most often follows an acute myocardial infarction or results from severe multisystem disease; the most common arrhythmias encountered are asystole, bradyarrhythmia, and electromechanical dissociation. In nonhospitalized patients, conversely, ventricular fibrillation is the most common arrhythmia and it typically reflects chronic myocardial ischemia associated with multivessel atherosclerotic coronary artery disease, rather than acute myocardial infarction. Survival after cardiac arrest and cardiopulmonary resuscitation generally ranges from 10% to 20% and is similar for both hospitalized and nonhospitalized patients. Individuals who are most likely to be resuscitated successfully include patients with witnessed sudden arrest caused by ventricular fibrillation outside the hospital when electric countershock can be performed within seven to eight minutes; hospitalized patients with primary ventricular fibrillation and ischemic heart disease; those with cardiac arrest in the absence of life-threatening coexisting conditions, such as oliguria, metastatic cancer, sepsis, pneumonia, or acute stroke; and patients with hypothermia, drug overdose, airway obstruction, or primary respiratory arrest. The author reviewed the diagnosis and management of cardiopulmonary arrest, advanced cardiac life support, and controversies about drug therapies. He concluded that "after more than 30 years of widespread use of CPR, a reevaluation of its benefits in terms of survival and quality of life shows it to be a desperate effort that will help only a limited number of patients. For most, CPR is unsuccessful. Although potentially lifesaving, it will continue to present ethical dilemmas for medicine and society."—George B. Bartley

*Department of Emergency Medicine, Harbor-UCLA Medical Center, 1000 W. Carson St., Torrance, CA 90509.

Half a loaf is better than waiting for the bread truck. A computerized mini-medical record for outpatient care. Carey, T. S.*, Thomas, D., Woolsey, A., Proctor, R., Philbeck, M., Bowen, G., Blish, C., and Fletcher, S.: Arch. Intern. Med. 152:1845, 1992.

We describe a locally developed system for partial computer storage of medical data, called the mini-medical record system. The system produces a typed face sheet prior to each patient visit. The face sheet, which also serves as a progress note, contains patient demographic data, medical problem lists, previous vital signs, allergies, medication profile, and health maintenance reminders. Between regularly scheduled visits, all computerized data are available by computer printout for unscheduled visits to walk-in clinics and the emergency department. Structured reports are generated by the system that describes each resident and faculty members' practice. Quality assurance reports are also available. Since the system draws from several already existing databases, new data entry requirements are modest and cost to the institution is low. Partially computerized systems can be developed inexpensively and are well received in multispecialty practices, where interphysician communication is vital.—Authors' abstract

*Division of General Medicine and Clinical Epidemiology, University of North Carolina, Division of General Medicine, CB 7110-5039 Old Clinic Bldg., Chapel Hill, NC 27599-7110.

Truth telling to the patient. Surbone, A.*: JAMA 268:1661, 1992.

The author, an oncologist who has practiced both in the United States and Italy, described the differences between the two countries regarding the disclosure of medical information to patients. Whereas "many Americans usually demand and are given information that enables them to make decisions either autonomously or with a physician's advice," Italian patients "are not always informed of their diagnosis and prognosis," a practice that does not violate the Italian Deontology Code. Because in Italian culture a patient's autonomy often may lead to his isolation, withholding information may be considered by the physician to be in the patient's best interest and therefore may be deemed to be ethically proper. The number of medical malpractice lawsuits is increasing rapidly in Italy, however, and the author fears that "physicians may communicate vast amounts of complicated information to unprepared patients only out of fear of litigation," which "will not improve the patient-physician relationship." Because "Italian society is not prepared for the American way" that encourages complete

disclosure, the author concluded that "since. . . the suffering person knows the truth,. . . the only way to respect both Italian ethical principles and the patient's autonomy and dignity is to let the patient know that there are no barriers to communication and to the truth."—George B. Bartley

*Department of Oncology, Santa Chiara Hospital, Via Roma 67, Pisa, Italy.

Is truth telling to the patient a cultural artifact? Pellegrino, E. D.*: JAMA 268:1734, 1992.

Although "what is beneficent in one country may seem maleficent in another country," the author postulated that medical ethics is not a cultural artifact and based his conclusion on an understanding of patient autonomy. Autonomy, which "has tended to become a moral absolute" in the United States, is an equal prima facie principle with nonmaleficence, beneficence, and justice and thus has no "a priori moral hegemony over the others." Patients, however, may exercise their autonomy by delegating (either explicitly or implicitly) decision-making authority to others, an act that legitimately may be influenced by the circumambient culture. The author proposed that physicians, in rare circumstances, may withhold the truth if there is "substantial evidence that offering the patient the truth has significant probability of causing harm." To preserve both autonomy and beneficence, "physicians must get to know their patients well enough to discern when, and if, those patients wish to contravene the mores of the prevailing medical culture. This requires a degree of familiarity and sensitivity increasingly difficult to come by, but morally inescapable for every physician who practices in today's morally and culturally diverse world society."—George B. Bartley

*The Center for Advanced Study of Ethics, Georgetown University, Washington, DC 20057.

NEWS ITEMS

Send News Items to
American Journal of Ophthalmology
435 N. Michigan Ave., Suite 1415
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The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

XXVII International Congress of Ophthalmology

The XXVII International Congress of Ophthalmology will be held June 26–30, 1994, in Toronto, Ontario, Canada. Registration will be all day Saturday and Sunday, June 25 and 26. The exhibition opens Sunday, June 26, and there will be a president's reception on Sunday. On Monday, June 27, there will be parallel symposia on AIDS, retinal surgery, glaucoma, inherited retinal dystrophies, and uveitis. On Tuesday, June 28, there will be parallel symposia on glaucoma, corneal and external disease, contact lenses, cataract and implant surgery, retinoblastoma and uveal melanoma, and orbital disease. On Wednesday, June 29, the program will focus on prevention of blindness throughout the world with strategies for appropriate and cost-effective eye care. On Thursday, June 30, there will be parallel symposia on pediatric ophthalmology, telemedicine and computerization and imagery, medical and surgical pharmacology, and vitrectomy.

Officially accepted satellite meetings include the following: Ergoophthalmological Internationalis, the European International Society of Ophthalmology, Traditional Chinese Medicine, the Combined Meeting of Federated Corneal Societies, the Castroviejo Cornea Society, the International Conference on Myopia, the International Conference on Ophthalmic Photography, the International Glaucoma Society, the International Intraocular Implant Club, the International Medical Contact Lens Symposium, the International Oncology Conference, the International Refractive Surgery Club, the International Society of Genetic Eye Disease and Retinoblastoma Society, the International Society of Ocular Fluorophotometry, the International Society of Ophthalmic Pathology, the International Society of Refractive Keratoplasty, the International Symposium on Eyelids, the Orbit and Lacrimal System, the International Symposium on Fluorescein Angiography, the International Symposium on Ocular Microsurgery, and the Medical Eye Safety Association, the University of Toronto Department of Ophthalmology Research Day, and the Volunteer Eye Surgeons Association.

For more information, write the Congress Secretariat, International Congress of Ophthalmology, 275 Bay St., Ottawa, Ontario, Canada K1R 5Z5; telephone (613) 829-0084; fax (613) 829-1561.

Czech and Slovak Societies for Ophthalmology and First Clinic of Ophthalmology: Scientific Meeting of Young Ophthalmologists

The Czech and Slovak Societies for Ophthalmology and the First Clinic of Ophthalmology of Brno Masaryk University will cosponsor a scientific meeting of young ophthalmologists April 2 and 3, 1993, in Brno, Czechoslovakia. For further information, write Květa Kvapilíková, Ph.D., 1st Clinic of Ophthalmology, St. Anna Hospital, Pekařská St. 53, 65691 Brno, Czechoslovakia; telephone 42 5 318 2844; fax 42 5 331474.

Henan Eye Trauma Institute: Second International Ocular Trauma Conference

The Henan Eye Trauma Institute will hold its Second International Ocular Trauma Conference April 9–13, 1993, in Zhengzhou, Henan, People's Republic of China. For more information, write Zhang, Ziaofang, M.D., P.O. Box 10507, Zhengzhou, Henan 450052, People's Republic of China; telephone 86-371-664217; fax 86-371-664217.

International Society on Metabolic Eye Disease: Ninth Symposium

The Ninth Symposium of the International Society on Metabolic Eye Disease will be held Sept. 19–22, 1993, in Herzliya, Israel. For further information, write Heskel M. Haddad, M.D., 1125 Park Ave., New York, NY 10128; telephone (212) 427-1246; or write Gideon Riv-

lin, Kenes, Israel Industry House, 29 Hamered St., Tel Aviv, Israel 68125.

Singapore National Eye Centre: First International Meeting

The Singapore National Eye Centre will hold its First International Meeting April 16–18, 1993, in Singapore. For further information, write The Administrator, Singapore National Eye Centre, 11 Third Hospital Ave., Singapore 0316; telephone (65) 227 7255; fax (65) 227 7290.

University of Heidelberg: Laser Scanning Ophthalmoscopy, Tomography, and Microscopy

The Department of Ophthalmology at the University of Heidelberg will hold its Fourth International Meeting on Laser Scanning Ophthalmoscopy, Tomography, and Microscopy May 20 and 21, 1993, in Heidelberg, Germany. For more information, write Reinhard O. W. Burk, M.D., Universitäts-Augenklinik, INF 400, W-6900 Heidelberg, Germany; telephone (06221) 56-6604; fax (06221) 56 54 22.

American Society of Outpatient Surgeons: 14th Annual Meeting

The American Society of Outpatient Surgeons will hold its 14th Annual Meeting Feb. 18–21, 1993, in San Diego, California. For more information, write Michelle Tompkins, American Society of Outpatient Surgeons, 4805 Mercury St., Suite E, San Diego, CA 92111-2110; telephone (619) 279-1325.

Eye Foundation of Kansas City: 16th Midwest Glaucoma Symposium

The Eye Foundation of Kansas City will sponsor the 16th Midwest Glaucoma Symposium, Stepping into the 21st Century, March 27 and 28, 1993, in Kansas City, Missouri. For additional information, write Sue Dunphy, CME Coordinator, Eye Foundation of Kansas City, 2300 Holmes, Kansas City, MO 64108; telephone (816) 881-6153; fax (816) 881-6167.

Manhattan Eye, Ear & Throat Hospital: Medicare Coding and You—Getting it Right the First Time

The Department of Ophthalmology of the Manhattan Eye, Ear & Throat Hospital will sponsor a course, Medicare Coding and You—Getting it Right the First Time, March 6, 1993, in New York City. For more information, write Kimberly Corbin, Department of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3760; fax (212) 753-7699.

Mayo Clinic Scottsdale: Third Annual Ophthalmic Reviews

The Mayo Clinic Scottsdale will sponsor the Third Annual Ophthalmic Reviews March 25–27, 1993, in Phoenix, Arizona. For further information, write Trish Gean, Office of Medical Education, Mayo Clinic Scottsdale, 13400 E. Shea Blvd., Scottsdale, AZ 85259; telephone (602) 391-7447.

Mericos Eye Institute: Seventh Annual Visions in Ophthalmology Symposium

The Mericos Eye Institute of Scripps Memorial Hospitals will sponsor the Seventh Annual Visions in Ophthalmology Symposium Feb. 26 and 27, 1993, in La Jolla, California. For further information, write Sheila Seid, 3030 Children's Way No. 402, San Diego, CA 92123; telephone (619) 974-6780.

New York Eye and Ear Infirmary: Keratorefractive Surgery

The New York Eye and Ear Infirmary will sponsor a course on Keratorefractive Surgery Jan. 23, 1993, in New York City. For further information, write The Institute for Continuing Medical Education, New York Eye and Ear Infirmary, 2nd Ave. at 14th St., New York, NY 10003; telephone (212) 979-4430 or (212) 979-4444; fax (212) 979-4441.

Pittsburgh Ophthalmology Society and Pennsylvania Academy of Ophthalmology: Combined Meetings

The Pittsburgh Ophthalmology Society will hold its 29th Annual Spring Meeting and the Pennsylvania Academy of Ophthalmology will hold its Annual Scientific Meeting March 18–20, 1993, in Pittsburgh, Pennsylvania. For additional information, write Mrs. Pat Kennerdell, 2545 Mosside Blvd., Monroeville, PA 15146; telephone (412) 243-8845.

Stanford University: Sixth Annual Ophthalmology Course—Updates and Workshops for the Clinician

The Department of Ophthalmology at the Stanford University School of Medicine will hold the Sixth Annual Ophthalmology Course—Updates and Workshops for the Clinician May 15, 1993, in Stanford, California. For further information, write Mark S. Blumenkranz, M.D., Director, CME, Department of Ophthalmology A-157, Stanford Medical Center, Stanford, CA 94305-5308; telephone (415) 725-7269.

Stanford University: Surgery and Laser of the Macula—New Treatments for Old Diseases

The Department of Ophthalmology at the Stanford University School of Medicine will sponsor a course, Surgery and Laser of the Macula—New Treatments for Old Diseases, April 3, 1993, in Stanford, California. For further information, write Mark S. Blumenkranz, M.D., Director, CME, Department of Ophthalmology A-157, Stanford Medical Center, Stanford, CA 94305-5308; telephone (415) 725-7269.

Texas Tech University: Fourth Annual Research Symposium

The Department of Ophthalmology and Visual Sciences at the Texas Tech University Health Sciences Center will hold its Fourth Annual Research Symposium June 11 and 12, 1993, in Lubbock, Texas. For more information, write Andrea J. Adkins, Department of Ophthalmology, Texas Tech University Health Sciences Center, Lubbock, TX 79430; telephone (806) 743-2412; fax (806) 743-1782.

Utah Ophthalmological Society: Annual Winter Meeting

The Utah Ophthalmological Society will hold its Annual Winter Meeting Feb. 12 and 13, 1993, in Salt Lake City, Utah. For additional information, write Sue Vicchrilli, Utah Ophthalmological Society, 540 E. Fifth St. S., Salt Lake City, UT 84102; telephone (801) 355-7477; fax (801) 531-0381.

Virginia Society of Ophthalmology: Annual Meeting

The Virginia Society of Ophthalmology's Annual Meeting will be held May 21 and 22, 1993, in Norfolk, Virginia. For further information, write Donna Scott, 4205 Dover Rd., Richmond, VA 23221; telephone (804) 353-2721; fax (804) 355-6189.

Washington National Eye Center: Laser Surgery of Ocular Disease Symposium

The Washington National Eye Center and the Department of Ophthalmology of the Washington Hospital Center will cosponsor a symposium, Laser Surgery of Ocular Disease, March 26 and 27, 1993, in Washington, D.C. For more information, write Penelope A. Helfgott, WNEC, Suite 6B-13, 110 Irving St. N.W., Washington, DC 20010-2975; telephone (202) 877-6982.

Wills Eye Hospital: 45th Annual Conference

The Wills Eye Hospital 45th Annual Conference will be held April 1–3, 1993, in Philadelphia, Pennsylvania. For further information, write Jeanne Coughlin, Meeting Manager, 1621 Norristown Rd., Maple Glen, PA 19002; telephone (215) 322-8950.

Wilmer Ophthalmological Institute: 52nd Wilmer Residents Association Meeting

The Wilmer Ophthalmological Institute's 52nd Residents Association Meeting will be

held April 29–May 1, 1993, in Baltimore, Maryland. For more information, write Laura Sheldon Stover, Wilmer 303, Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21287-9255; telephone (410) 955-2830.

New York Society for Clinical Ophthalmology: New Officers

The New York Society for Clinical Ophthalmology has selected the following new officers: Frederick M. Wang, president; Dorothy N. Friedberg, chairman, Program Committee; Stanley Chang, chairman, Membership Committee; Thomas O. Muldoon, treasurer; Ronald M. Burde, recording secretary; Andrew M. Prince, corresponding secretary; and Kevin C. Greenidge, historian.

Institute of Ophthalmology: Ashton Building Opening

Oct. 14, 1992, the Duke of York unveiled a plaque commemorating the official opening of the Ashton Building of the Institute of Ophthalmology, London. The building honors Professor Norman Ashton, C.B.E., F.R.S., who has served the Institute of Ophthalmology since its founding in 1948. The Institute has a staff of nearly 200 and is the principal beneficiary of the Fight for Sight, which has guaranteed £2 million in research funds to the Institute over the next five years.

The new building, on Bath Street, permitted the consolidation of the Institute so that all activities are next to Moorfield's Eye Hospital. The Fight for Sight contributed over £3 million toward staffing and equipment. The new building provides a modern, scientific environment that brings together the Institute and the Hospital and provides more effective transfer of laboratory findings to the treatment of patients.

Personals

Leonard Apt and Sherwin Isenberg

Leonard Apt and Sherwin Isenberg, professors of ophthalmology at UCLA Jules Stein Eye Institute, received the first Escalon Science Award from Escalon Ophthalmics, Inc., Skillman, New Jersey. The award, which was present at the 1992 American Academy of Ophthalmology meeting, was in recognition of their pioneering research in the field of presurgical ophthalmic antisepsis.

Bernard K. K. Fung

Bernard K. K. Fung of the Jules Stein Eye Institute and the University of California, Los Angeles, has been selected as recipient of the Alcon Award by the Alcon Research Institute. The award will provide Dr. Fung with $100,000 for research in ophthalmology. He is conducting research into retinal phototransduction, the process whereby light received by visual cells triggers chemical changes that ultimately generate electrical signals to the brain.

John W. Simon

John W. Simon, professor of ophthalmology and pediatrics at Albany Medical College, has been named chairman of the Department of Ophthalmology. He served as acting chairman of the Department since November 1991. Dr. Simon is a graduate of Colgate University and the Mt. Sinai School of Medicine. He served his residency at Mt. Sinai Medical School and was a Fellow in Pediatric Ophthalmology at Wills Eye Hospital. Dr. Simon is a director of the American Association for Pediatric Ophthalmologists and Strabismus, a member of the Public Information Committee of the American Academy of Ophthalmology, and a member of the Medical Advisory Committee of the New York State Commission for the Blind.